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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
April 19, 2006
Marriott Hotel Seatac
9:00am – 4:00pm

Committee Attendance:
Angelo Ballasiotes, Pharm D
Robert Bray, MD
Carol Cordy, MD (Vice Chair)
Jason Iltz, Pharm D
Janet Kelly, Pharm D
Daniel Lessler, MD (Chair)
T. T. Vyn Reese, M.D.
Patti Varley, ARNP
Kenneth Wiscomb, PA-C

9:00 a.m. - Committee came to order.

P&T Meeting
June 21, 2006

Tape 1 of 3

Dan Lessler: Today we're actually being filmed, I guess, by WTV. So I was going to ask if people that are sitting around the table perhaps could just introduce themselves. That would be helpful. And I think probably if we could start down at that end. Thanks.

Andre Rossi: My name is Andre Rossi. I'm with the Department of Corrections.

Siri Childs: I'm Siri Childs. I'm the Pharmacy Policy Office Chief with HRSA(?).

Jaymie Mai: Jaymie Mai, Labor and Industries.

Doug Tuman: Doug Tuman, Labor and Industries.

Carol Cordy: Carol Cordy, P&T Committee Member.

Janet Kelly: Janet Kelly, P&T Member.

* For copies of the official audio taped record of this meeting, please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

Angelo Ballasiotes: Angelo Ballasiotes, P&T Committee Member and Central Washington Comprehensive Mental Health in Yakima.

Ken Wiscomb: Ken Wiscomb, P&T Committee Member.

Vyn Reese: Vyn Reese, P&T Committee Member.

Dan Lessler: Dan Lessler, Chair of the P&T Committee.

Bob Bray: Bob Bray, P&T Committee Member.

Jason Iltz: Jason Iltz, P&T Committee Member.

Alvin Goo: Alvin Goo, P&T Committee Member.

Jeff Graham: Jeff Graham, Health Care Authority.

Nancy Fisher: I'm Nancy Fisher, Medical Director of Health Care Authority.

Ray Hanley: Ray Hanley, Health Care Authority.

Duane Thurman: Duane Thurman, Health Care Authority.

Erika Clayton: And Erika Clayton, Health Care Authority.

Dan Lessler: Thank you. So I believe we have…is Dana Sullivan on the phone?

Dana Sullivan: Yes, I am.

Dan Lessler: Hi Dana, this is Dan Lessler. Welcome. What we do here is we're going to project your PowerPoint and I'll let you know when it's up in just a second and then we'll let you take it from there. We're just…give us a second here. There it is. So we are looking at the…your title slide and you can just take it from there. We'll move the slides as you want. We can get going. Does that sound okay?

Dana Sullivan: That's fine. Just note that I can hear you sort of in the background. So I hope you can hear me well. If you have to say something it will have to be…I could hear Jeff Graham very well before, but you're a little bit further away. So you might have to repeat a few questions if you…

Dan Lessler: Okay. We'll have people speak up. We can hear you very well. So you're all set.

Dana Sullivan: Shall I go ahead and get started?

Dan Lessler: Yes.

Dana Sullivan: Okay. Well, I was at the Omni Drug Class Review for nasal corticosteroids. I guess you can just go ahead and go to the next slide. I'll go ahead and start with the search strategy. It's the basic EPC search strategy. We looked in Cochrane

Central Register of controlled trials and MEDLINE and that was fourth quarter of 2005 and then the MEDLINE search was 1966 to October week three 2005 just to note when we did this. The pharmaceutical company submissions we received from mometasone, fluticasone and budesonide. You can see that we looked in resident lists and we also looked at FDA reviews.

Next slide. A quick review of our process of data collection and analysis. The slides are assessed…or the studies are assessed for inclusion and then they are quality rated using pre-defined criteria that you can find in the…probably in the report and the EPC. The study dated abstracted, the qualitative synthesis of data is done in meta-analysis if possible. In our case that wasn't possible and the overall grade of the other allocated for the body of evidence for each key question. So key question one, two and three. And you can find that information in the back and I'll talk about it at the very end of the summary.

Next slide, please. The inclusion criteria – we looked at the populations of adult patients and children under 18 in outpatient settings with the following diagnosis: seasonal allergic rhinitis, perennial allergic rhinitis, and non-allergic rhinitis. With seasonal being mostly pollen or trees, grass and things like that. Perennial being dust mites, molds and animal air. Perennial sometimes is also pollen in certain areas of the globe. So we have that kind of with the south and things. There's also…in the perennial is also included mixed allergic rhinitis. Some of the studies included the percentage of patients that had both seasonal and perennial and some of them didn't. So we didn't focus on that. We basically put them in the perennial. And the non-allergic rhinitis is basically the diagnosis of exclusion.

Let's move on to the next slide. The interventions that we looked at was or were mometasone also known as Nasonex, fluticasone, budesonide, triamcinolone, beclomethasone and flunisolide and throughout the studies we found that some of the aerosol versions were still in some of the studies so we talk a little bit about the old and the new formulations. For example, of flunisolide. And so we'll move on to the next slide.

We looked at efficacy outcomes. As usual with the EPC we look at symptomatic relief and that was measured mostly in total nasal symptom score, usually on a 4-point scale of 0 to 3 with 0 being none and 3 being severe. They looked at…usually they would group them together—congestion, sneezing, itching and [inaudible]. And they would then give total nasal symptom score. Sometimes they gave the individual one and often times the ocular symptoms were also noted. We also looked at onset of action and quality of life improvements.

Next slide. The safety outcomes – we looked at safety outcomes, overall adverse event reports, withdrawal to adverse events, serious adverse events reported and then specific adverse events. And so I kind of want to think about it in terms also of local adverse events being dryness, [inaudible], irritation and local infection and then we have the more serious systemic adverse events being gross depression in children, ocular adverse events and hypercorticism. And they are listed…the other specific adverse events are listed there.

Next slide. Study design – for effectiveness or efficacy we looked at controlled clinical trials and good-quality systematic reviews, which we didn't find any in this case. So there were no symptomatic reviews included. For adverse events we also included observational studies.

Next slide, please for the results. And here's an overall review just sort of to give you a picture of what we found. We didn't find effectiveness trials. We did find 36 head-to-head trials. Of those 16 looked at seasonal allergic rhinitis, 20 looked at perennial or mixed allergic rhinitis and there were none for non-allergic rhinitis. We also found 21 placebo-controlled trials. Those were included when we didn't have any trials and we basically tried to do indirect comparisons, which weren't successful, but I'll talk about that a little bit later for the various reasons. We used 9 for seasonal rhinitis in children, 10 in perennial rhinitis and then 2 for adult non-allergic rhinitis. We also included 4 observational studies.

Next slide, please. Okay. This is an overview of the information that we found for seasonal allergic rhinitis and this is focusing on both adults and children. It's just an overview of the drug comparisons that we found. We found drug comparisons for adults. Beclomethasone versus flunisolide, triamcinolone, fluticasone, mometasone and budesonide. So beclomethasone being one of the older drugs had been compared to many. Fluticasone versus triamcinolone. Budesonide versus fluticasone and then there's also a brief statement about the old versus the new version of flunisolide for adverse events. We only found one direct comparison for children with seasonal allergic rhinitis. That was beclomethasone versus mometasone and the indirection comparisons for children…the outcomes reported or the outcomes we actually studied were similar, but the outcomes reported were reported in such a way that we couldn't look across all the studies and do an indirect comparison. In the subpopulations, which was key question three also provided insufficient evidence to make comparisons between the drugs.

Next slide, please. Details on the adult placebo allergic rhinitis we found no significant differences for improvements of rhinitis symptoms. The outcomes were generally reported in physician rated global evaluation of improvements and/or percent change in the total symptom. Table 5 in the text, if you want to make a note, on page 16 is a really good place to go ahead and look back at the summary of all of this. And the quality of life outcomes were rarely reported in head-to-head trials. In this case the beclomethasone, fluticasone and triamcinolone that were studied that we found were associated with similar levels of improvement. So there were no differences there in the quality of life. There few quality of life reports that we did get. And that's also summarized in Table 6 on page 17. So you might want to go back and look at that later.

Next slide. Seasonal allergic rhinitis in children – the one head-to-head trial that I mentioned studied 679 children over four weeks comparing mometasone to beclomethasone and showed no significant difference in mean reduction of physician-rated total nasal symptom score. The physician-rated was done on the basis of the diary that they submitted. So it's not just a physician saying what symptoms the child had. And there was no difference in adverse event. In addition to evidence from the 9 placebo-controlled trials, which are summarized in Table 7

on page 19, had insufficient…they were insufficient for assessing comparative effects for the reasons that I previously mentioned.

Okay, next slide. We found one study of rhinitis prophylaxis in adults and mometasone did…is the drug that is used for that. In this case mometasone was superior to beclomethasone in preventing rhinitis symptoms during pre- and peak-season, but mometasone prophylaxis was also associated with significantly higher rates of headache. The headache rates are 63% for mometasone, 51% for beclomethasone and then 52% for placebo. So they were similar, but definitely they reported some difference. I'm trying to think…I wanted to kind of define the prophylaxis and they defined it as the proportion…no, the lower means total system score from baseline to season start. So that's what they are measuring. They are measuring that time before the season begins and saying mometasone showed to be superior to that.

Go to the next slide. And now we're switching to perennial allergic rhinitis and this is an overview. There is also a table…Table 9 on page 22 that has an overview of that and for efficacy and adverse effects the direct comparison for results were beclomethasone versus fluticasone and mometasone, fluticasone versus mometasone, budesonide versus fluticasone and mometasone and then the old and new formulations of flunisolide. And that, again, will come into play when we talk about the adverse effects. The indirect comparisons since there were no direct comparisons for triamcinolone looked at some placebo studies and again were unable to compare across the studies because of the heterogeneous outcome recording. For children there was one study – beclomethasone versus fluticasone and again we tried to do some indirect comparisons and they were also insufficient for comparing efficacy. The subpopulations as with seasonal allergic rhinitis also provided insufficient evidence.

Next slide, please. For adults with perennial allergic rhinitis there were very few differences found. Actually, only in one trial…efficacy there were no differences in adverse events and the one difference in efficacy that we found was in a head-to-head trial of 273 people over 6 weeks. It was a Canadian and Spanish trial and they found budesonide at 256 mcg dose to be associated with a significantly greater mean point reduction in combined nasal symptom score when compared to fluticasone at 200 mcg and you can see there the point reduction on a scale of 0 to 4 or 0 to 4, yeah, because it has 4 total. The point reduction for budesonide was reduced by 2.11 versus 1.65 and the P values are included. So it wasn't dramatic but it was significant and that's what they found. There was no comparative evidence for the new formulation of flunisolide. We only found the old formulation that they reported on.

Let's go to the next slide. In children with perennial rhinitis and you can see that Table 11 on pages 26 and 27 there is a summary of the placebo trials. There was the one head-to-head trial of 120 children over 12 weeks and fluticasone was found to be as effective as beclomethasone. In mean percent increase of symptom-free days for all symptoms. So they are not measuring the total nasal symptom score, they are measuring symptom free days. And there was no difference in adverse events for children in the comparisons. And the evidence from the 10 placebo-

controlled trials again was insufficient for assessment of comparative effects for the same reasons that I mentioned earlier.

Next slide, please. Non-allergic rhinitis – there wasn't much evidence here. There was no comparative evidence for adults with non-allergic rhinitis. We found two placebo-controlled trials, I think, of fluticasone and mometasone, but the outcomes were reported just so that we couldn't compare efficacy across the studies. With children there were no…neither head-to-head trials nor were there any placebo-controlled trials in the study of non-allergic rhinitis.

Next slide. Okay, and this is basically an overview of key question two looking at the adverse events. First we're going to talk about adults. Generally, there was no significant difference in comparative rate withdrawals due to adverse events and less serious adverse effects. I had mentioned before those were more the local adverse effects—headache, throat soreness, epistaxis and nasal irritation, when the drugs were compared at similar doses. The old formulation of flunisolide was found to have significantly higher rates of nasal burning and stinging than beclomethasone AQ. That comes as no surprise and the newer formulation of flunisolide in two head-to-head trials within patients with seasonal allergic rhinitis. So that's just a note on the comparisons—the old to the new formulations.

Go to the next slide. More serious harms in adults – there was one very large British study. It was a retrospective cohort study looking at relative risk of cataract among beclomethasone compared with those who didn't take anything at all, who were unexposed. And they found a relative risk of .8. So there was no increase in cataract incidence there. There was also no evidence about glaucoma or glaucoma associated adverse events.

Next slide. The children…the serious adverse events or the systemic adverse events in children are summarized in Table 12 on page 34 and that will give you a really good overview of what they were actually measuring because often times growth is measured in height increase, sometimes it's measured with a [inaudible] meter and sometimes it's measured just with a regular measure…the way they measure at the pediatrician. So with growth retardation there were some differences. We found one placebo-controlled trial of 12 months – beclomethasone that was associated with significantly lower height increases. Increases of 5 versus 5.9 cm. So they measured the kids over 12 months and these children are usually school children. You can see on Table 12. I don't have it open myself, but on Table 12 they have the age of the children studied. And there was one retrospective observational study done. Over three years they went back and looked at children who were taking beclomethasone and found that the height increases were similar to expected, but it wasn't a controlled trial. It was a retrospective observational trial and two placebo-controlled trials of fluticasone and mometasone found no significant different in growth and I believe if I'm looking at my table correctly that those difference were also measured similar to the other placebo-controlled trial as in height increase over time. So they compared not just effected height, but height increase. So you can see that and take a little bit closer look at it later.

Ocular adverse effects – in one uncontrolled retrospective trial budesonide was associated with the development of two cases of transient lenticular opacities. And the clinical significance of the opacities was not reported. It's not clear to us what they exactly mean by transient, but we thought we would report that because they reported it in the trial.

Let's go on to the next slide. And this is basically a summary of the findings and you could also find on page 38 and 39, Table 13, the strength of the evidence for each one of these key questions and each one of these bodies of evidence for seasonal allergic and perennial allergic rhinitis. But to make it a little bit simpler I just reported it so and we'll go through it. For seasonal allergic rhinitis in adults there was no evidence of difference in efficacy or adverse events. For prophylaxis of seasonal allergic rhinitis in adults mometasone was found to be superior to beclomethasone, but associated with a risk of increased headache…or increased risk of headache. For perennial allergic rhinitis in adults budesonide was found to be superior to fluticasone in one trial in reducing rhinitis symptoms in one fair quality trial with no difference in adverse events. All other comparative evidence found no significant difference in efficacy or adverse events for those…for that population.

Next slide. Non-allergic rhinitis in adults – there was only indirect comparative evidence that provided no conclusive information about efficacy and/or safety due to heterogeneity of the outcome reporting. And cataracts – there was no difference in relative risk among beclomethasone versus non-users from one observational trial.

Next slide, please. For the subgroups there was no evidence or the evidence was insufficient to make any conclusions about comparative effectiveness, efficacy or safety in subgroups based on demographics, concomitant use of other medications, co morbidities or pregnancy.

Next slide. The summary findings in children – for seasonal allergic rhinitis there were no differences in indirect…direct or indirect comparisons found for efficacy or safety. The same goes for perennial rhinitis and non-allergic rhinitis in children there was no evidence found.

The serious harms or serious adverse effects – growth retardation in children. Beclomethasone was significant. It was found to have a significantly lower increase in one placebo-controlled trial and similar to expected height increases in one retrospective observational study. Mometasone and fluticasone showed similar height increases relative to placebo. And all three of those were placebo trials were 12 months.

The ocular adverse events – budesonide as mentioned previously was associated with two cases of transient lenticular opacities in one uncontrolled retrospective study. And the clinical significance in this case was not reported. And that was the first report of the morning. Do you have any questions?

Dan Lessler: Dana, can you hear me? No. Dana, thanks, that was very good. What we're going to do is just open it up for questions from P&T Committee Members for you, Dana, in terms of your presentation. So I'll ask if there are specific questions to be addressed to Dana from members of the committee at this point.

Vyn Reese: This is Dr. Reese. I think one of the problems with these studies is some are older formulations and the doses are different between the two substances that are checked or are compared to each other and the newer formulations are different and their tolerabilities are different. So I think the data is very confusing in this group. It looks like there really is no significant differences in these [inaudible]'s as far as we can tell from the studies that have been presented here. Is that a correct assessment?

Dana Sullivan: I'm sorry, could someone near the microphone repeat the question? I can hear you not so well.

Vyn Reese: The question is given that several of these studies are done with older formulations, the doses often aren't equivalent between the older and the new…

Dana Sullivan: I'm sorry, I'm sorry, I still can't hear very well. Sorry. I don't know if someone…

Dan Lessler: Can you hear me?

Dana Sullivan: Yes, I can hear you.

Dan Lessler: Okay. We're going to try a different microphone here.

Vyn Reese: This is Dr. Reese, can you hear me?

Dana Sullivan: Yes.

Vyn Reese: Okay. The question is, given that several of these comparative trials were done with older formulations and the doses were often not equivalent between the two agents studied, is there really any…can you really state if there is any difference at all between these agents in efficacy as far as the data that's been presented today is concerned? It doesn't look like it from what you said.

Dana Sullivan: Okay, I'm so sorry, you definitely are breaking up. I don't know…sorry…so to repeat just the question. So this old and new formulations I got.

Vyn Reese: Right. Based on your findings it looks like there is no difference in efficacy in the studies that you've reviewed between these agents in a variety of indications. Is that correct?

Dana Sullivan: Right.

Vyn Reese: Okay. And my other question is the growth retardation in children there's two different trials and one sort of contradicts the other. How do you feel about that evidence?

Dana Sullivan: Well, the trials that contradict each other are…as I mentioned, one is a placebo-controlled trial. You can look on page…do you all have the report?

Vyn Reese: On my computer at home.

Dana Sullivan: Oh, okay.

Vyn Reese: I read the report, right, but I don't have it here.

Dana Sullivan: Okay. No one has the report, but on page 34 there's Table 12. You can always make a note of that and look at it, but the trials of beclomethasone for example that contradict each other, one is a three-year long retrospective trial with 60 children with an average age of 5.8 years, but basically they measure it differently. They look at…they compare the annual growth velocity compared with the predicted growth velocity. So that's one piece of evidence. And then the other evidence is a placebo-controlled trial of 80 children with an average age of 7.5 and 7.1 years for male and female. And they measured the mean change in height from baseline, which is a different measurement and it has a different…it has a different outcome. So, you know, you basically have to make a judgment here and we can't necessarily say, you know, you can say, "Okay, we've got the control trial and it gives us this evidence and then we have this other trial." It was actually done in response to the trial done…the first beclomethasone trial. So they wanted to basically make a statement and I can't…you'll have to kind of figure out how that works for you and what kind of evidence that gives you.

Vyn Reese: And one was a one-year trial and one was a three-year trial and they were for different age groups of children. So it's very confusing.

Dana Sullivan: Right. Right. Well, the one wasn't really a trial. It was just a retrospective [inaudible] study. So they went back and looked at the measurement of children that they had given beclomethasone to. So, you know, the other one was a prospective and one was a retrospective. So it's important to note that.

Vyn Reese: Thank you.

Dana Sullivan: I'm sorry. I can't say much more than that. I mean it speaks for itself I think also that mometasone did a similar 12-month trial and fluticasone and those didn't find any significant difference in…any change in height from baseline and that's what they were measuring. Any other questions?

Dan Lessler: Are there any other questions from committee members for Dana? Okay. Dana, if you can stay on the line just for a few more minutes here. I was going to ask…is there a stakeholder sign up list and…so Dana, at this point is what we do is allow stakeholders three minutes each to comment and if possible we would like you to stay on the line because sometimes questions arise as a result of those comments and it's helpful to have your expertise available. Does that sound okay?

Dana Sullivan: Do you mean for the next half an hour when you have the comments or…

Dan Lessler: No, actually, there are only two people signed up. We're talking maybe 10 to 15 minutes probably.

Dana Sullivan: Perfect. You let me know.

Dan Lessler: So the first stakeholder is Randy Legg from AstraZeneca. If you could limit your comments to three minutes, please. Thanks.

Randy Legg: I'll be less than that. Can you hear me okay? I better raise this. Is that better? The first comment I was going to answer the doctor's question about the growth velocities and what we find a lot in inhaled steroids studies is the growth velocity, if it's reduced, it's reduced in the first year and then after year one people on these medications tend to catch up. So that's the big difference in the one versus three-year study.

I just had a few comments about our drug from Rhinocort Aqua. The first thing is our drug is a once-a-day medication. The inhaler comes in a 120-spray canister. The starting dose is one spray per nostril once a day. So for people on maintenance doses they can get two months supply out of that canister and it is the only Category B FDA rated steroid. And I think that's it.

Dan Lessler: Thank you. Next is Dan Manning from Schering-Plough.

Dan Manning: Good morning. My name is Dan Manning. I'm with Schering-Plough Global Medical Affairs and I would like to thank the committee for giving me a few minutes to discuss the Nasonex or mometasone steroid nasal spray. Nasonex is [inaudible] free, alcohol free and one of the most commonly prescribed drugs in the nasal inhaled steroid class. As an established safety and efficacy profile in multiple indications. Nasonex has a broad range of indication including the treatment of nasal symptoms and seasonal allergic rhinitis and perennial allergic rhinitis in adult and pediatric patients down to two years of age, which is the lowest in the anti-[inaudible] class. It also is the only anti-[inaudible] proof for prophylaxis of nasal symptoms in patients 12 years of age and older for SAR. And it is also one of two NIS's approved for nasal polyp indication with Vancenase AQ. Clinical studies have shown Nasonex to be very safe. It has a low total systemic bioavailability less than 0.1%. Nasonex has shown no suppression without HB access. Nasonex is indicated for children under 2 years of age, which is the lowest in the NIS class and no growth suppression effects of Nasonex were found following pediatric studies for one. Really, in conclusion I just want to say that as an established efficacy and safety profile and multiple indications. Thank you.

Dan Lessler: Good. Thank you. Are there any questions or comments then from committee members? Great. So, Dana, thank you very much for your time. We appreciate it. We can let you go now.

Dana Sullivan: Okay. Thank you.

Dan Lessler: Bye, bye.

Dana Sullivan: Bye.

Dan Lessler: So either before we try to venture a motion here as we've been doing in the past what I'd ask is just for general comments or observations in response to the presentations regarding nasal corticosteroids from committee members and people who have any particular sense of this class of medications.

Vyn Reese: This is Dr. Reese. What [inaudible] these studies and these drugs it seems to me there is little to choose between them and the differences are fairly small. The pediatric…my only concern is the pediatric information and whether that would mean that we wouldn't want to have beclomethasone on the list. I think that's the only one there's a question about and that's even questionable. But data there is conflicting. It seems like these drugs are all safe and efficacious and I don't see a reason to pick one over the others. My only question is a safety concern about beclomethasone in children and that's the only concern I have about the drugs. The newer formulations are more tolerable than the old ones and are better tolerated by most patients. So it's a field influx and the drugs all work and the safety is pretty much the same across the line. The only question is the pediatric data in my view.

Dan Lessler: Alvin, yeah.

Alvin Goo: Hello?

Dan Lessler: You're on.

Alvin Goo: Okay. As far as the concern about beclomethasone in velocity of growth, um, the first study was a placebo versus beclomethasone and was for one year it only showed like a centimeter difference and then the other studies were basically, as mentioned before, three-year studies and showed no difference as far as beclomethasone versus…or between inhaled steroids. So as far as inhaled steroids in children there is slight reduction in growth, but it's during the first year and it's a centimeter and after that they catch up, but compared to beclomethasone and others there just hasn't been the study…a head-to-head study for side effects. So I think as far as beclomethasone goes it…velocity growth…growth velocity I don't think that there should be any major concern with that.

Bob Bray: This is Bob Bray. The concern I have about beclomethasone is that I think that the data is better that raised the concern than the comparative data that seemed to have to raise less concern. It was placebo-controlled and the beclomethasone study and the other studies that seemed to show less evidence were studies that looked at the comparison against predictive velocity. So I think it's reasonable to be concerned to some degree about beclomethasone. I guess the other issue, which may be more practical is that beclomethasone is indicated for age 6 and above, fluticasone is for age 4 and above, and mometasone is for age 2 and above. So the other two drugs that did not show the same growth concerns are actually indicated for younger age groups, which may give an advantage for those drugs on the pediatric end of it.

Dan Lessler: Thanks. Other comments? So it sounds like from what's been said so far that the drugs look quite equivalent in terms of safety and efficacy with the exception of beclomethasone and then there might be some special consideration or just a need to call out the availability of pediatric doses for younger kids. So if there aren't any…if there is no further discussion and having heard what we have so far I'm wondering if somebody would be willing to take a stab a motion to proceed with this.

Vyn Reese: This is Dr. Reese. I'll make an attempt here. After considering the evidence of safety, efficacy and special populations for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and non-allergic rhinitis, I move that mometasone, fluticasone, budesonide, triamcinolone, and flunisolide are safe and efficacious. No single medication is associated with fewer adverse events in special populations. The pediatric formulation needs to be included on the PDL. These drugs can be subject to therapeutic interchange on the Washington preferred drug list.

Dan Lessler: Any…

Janet Kelly: Janet Kelly. I guess I have a problem with excluding beclomethasone. I think there is one placebo-controlled trial that actually looked at it and we're ensuing because it's the only one that looked at it, it's the only one that has this problem and I don't think we can say that. Have the others done the placebo-controlled trial with measuring the same thing? They haven't. So we don't know that it doesn't have that same 1 cm growth retardation in the first year. So I think to single it out is really not what we should be doing here. I think that, yes, it's been noted, but I'm not sure that we can say that the others don't do that.

Dan Lessler: Didn't mometasone and fluticasone have similar height increases with the placebo and placebo-controlled trials? I think they did.

Bob Bray: This is Bob Bray. I think the other issue is that the other drugs that didn't study it don't have an FDA indication for under 11, I believe. So I think of the drugs that are indicated for that age group we're struck with that information. So I agree it's incomplete.

Vyn Reese: You know, I can include beclomethasone on the above list, it's just the pediatric formulation needs to be included. I think that's a fair way to do it. So let's just put beclomethasone in there and just say…the data for adults it's clearly not any different than what we have here. So it shouldn't be excluded for adults.

Dan Lessler: Do we need to define more what we mean by pediatric formulation in terms of…an FDA indication by age?

Bob Bray: This is Bob Bray. Before we type I guess what I would favor and see if everybody agrees, I would favor listing something like that fluticasone and/or mometasone must be in included for the pediatric age group. Does that sound reasonable?

Dan Lessler: And the reason for that being that they have the FDA indication down to the younger ages.

Vyn Reese: And they have the trials, too.

Dan Lessler: Yeah, then they have the trials as well. So why don't we edit this. [end of Side A]

Jason Iltz: This is Jason Iltz. My only comment was that there is a difference in terms of the approved ages. So I'm not sure if we're trying to cover the most people, which would be down to the age of 2. Then we would single out mometasone the and/or statement is fluticasone and that is actually approved for greater than 4 years of age.

Dan Lessler: So from what you're saying, Jason, it sounds like we would just…rather than having fluticasone or we would just put mometasone because then we capture the largest age…pediatric age range in terms of FDA indication. So maybe we can…it should be just mometasone there rather than fluticasone or mometasone. Are there other comments?

Carol Cordy: Carol Cordy. I was just looking through…all of them are approved for 6 and one is for age greater than 4 and then one down to 2. So I'm not sure we need to single one out at 6. Just to say that we should follow the FDA approved guidelines, because things could change. One of them may be approved for under 6 at some point. Again, I think we're leaving out the…which one was it for 4? Fluticasone…

Vyn Reese: I think we should go back and the more general pediatric formulation needs to be included and it's going to be different for different ages. I think when she starts splitting hairs it's going to be difficult. I mean for a 2-year-old the only one that's approved is mometasone. But if somebody's kid is 6 then there are more choices.

Dan Lessler: Bob, do you want to…

Bob Bray: Well, this is Bob Bray, again. I guess the only drug that we've singled out is the one that gets us the youngest FDA approved age. And there may very well be other drugs that wind up on the list from the…that would also be able to be chosen from depending upon how the list…the final list looks. So we wouldn't necessarily be eliminating other drugs. I just think that if we…if we make it too general and maybe this is a question for the rest of the folks from administration, but it seems to me like that isn't giving you enough guidelines to be able to understand what to choose and not to choose if it's just pediatric because that's a big white range.

Jeff Graham: This is Jeff Graham. I think that in the past we've given…you've given us…but we have to have a drug for pediatric indications and we've been able to fulfill that to requirement. So usually when you tell us that that's what we do. And we're looking at early pediatric…we're looking at children of all ages so we most likely, can't say for sure, pick one that would take children down to as low as we possibly can. I know we did that with the PPIs and so I know we've done it in the past and it would seem we could come up with a…a good result.

Vyn Reese: This is Dr. Reese. That way we wouldn't have to change this every six months as more drugs are added for that indication. I think that has the other advantage. It gives you a little more leeway as long as you use FDA approved. It's pretty clear it has to be an FDA approved pediatric formulation and that's changed with the PDI's as more of them become approved. It's something that's influx. It gives us more…like you said, a better handle on it until we review this class next year.

Nancy Fisher: This is Nancy Fisher. Can you hear me? I've been to [inaudible] pediatric formulation, excuse me, there are two pediatricians on staff that look out for the pediatric calculation.

Siri Childs: I think it would be fine from HRSA's perspective if you left it as FDA pediatric formulation also.

Dan Lessler: It sounds like a pretty strong consensus on that point. Okay. Any other…any other comments as people look at what we crafted here?

Vyn Reese: I can just re-read it, it's Dr. Reese, as the final motion. After considering the evidence of safety, efficacy and special populations for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, and non-allergic rhinitis, I move that mometasone, fluticasone, budesonide, triamcinolone, beclomethasone, and flunisolide are safe and efficacious. No single nasal steroids is associated with fewer adverse events in special populations. An FDA approved pediatric formulation must be included on the preferred drug list. Nasal steroids can be subject to therapeutic interchange in the Washington preferred drug list. Thanks.

Dan Lessler: Is there a second?

Ken Wiscomb: I second.

Dan Lessler: There's a second. Any other comments or discussion? Okay. All those in favor, please say I.

Group: I.

Dan Lessler: Opposed same sign. Okay. All right so the motion passes as written there. Thank you.

Where are we on our…what time do we have?

Dan Lessler: Next on our agenda is the comparative effectiveness of pioglitazone and rosiglitazone and actually Dr. Norris cannot be with us, but we do have her slide presentation so I'm going to walk us through that presentation and then we'll have discussion as we usually do.

So if we could have the first slide, please. These are the acknowledgements.

Next slide. The search strategy, again, looked to several databases to poll relevant articles as I think we're all accustomed to.

Next. The populations that were considered are those with type 2 diabetes, those with metabolic syndrome, and those with pre-diabetes. The medications that we're considering are pioglitazone or Actos, Rosiglitazone or Avandia.

Next. The primary outcomes that were looked at were A1c or fasting plasma glucose, time up to initiation of insulin, progression or occurrence of micro- or macrovascular disease, and quality of life.

Next. The inclusion criteria as far as study designs included efficacy or effectiveness studies, randomized controlled trials, or CCTs. I'm trying to…

Man: [inaudible]

Dan Lessler: Thank you. All quality categories were considered and conclusions were based on those studies that were classified as being fair to good and placebo controlled trials were also included. Subgroups were included if they had more than 10 patients included and adverse events included all study designs assuming they had more than 10 patients.

The data synthesis and analysis – qualitative component as well as quantitative through meta-analysis and application of usual meta-analysis methodology.

Next. The results of the search in type 2 diabetes there were 79 efficacy studies, 42 studies that I think related to adverse events, I believe what AE is referring to. Three head-to-head trials with respect to metabolic syndrome there were 4 efficacy trials, no studies looking at specifically adverse events and 1 head-to-head trial. And in pre-diabetes there were 4 efficacy studies, none looking at adverse events and 1 head-to-head trial.

The OHSU evidence based practice center did look at prior systematic reviews on this same topic. There were a total of 10 of which 4 were of fair to good quality. The conclusions from looking at this prior reviews were first there were no head-to-head randomized control trials that were included. Pioglitazone and rosiglitazone both appeared to effect a similar reduction in hemoglobin A1c of 1% and were well tolerated and there was not much data on long-term effects.

With respect to the first key question that was posed for patients with type 2 diabetes due to cortisone differs in their ability to reduce A1c levels first when used as monotherapy or then when added to other oral hypoglycemic agents.

Next. With respect to this question there are three fair quality trials—two trials between the…between group A1c difference was 0.1% in both trials and that did not reach statistical significance. There was one monotherapy and one…one of the trials was monotherapy and one was combined with glimepiride. One trial with no significant difference in A1c in either group.

Next. This is going to be sort of difficult to see. This is really a summary slide of head-to-head trials with respect to A1c. The upshot is that people can see there

with the bottom dark rectangular area indicates that because it crosses zero in terms of 95% confidence turnover is that it does not appear that there are any differences with respect to reduction of A1c between these two agents.

Next. We're now moving on to look at placebo-controlled trials and impact on A1c beginning with pioglitazone. There are 16 trials and looking at pooled results across…stratified by quality of study. There…the reduction in A1c was about 1 in fair to good quality and somewhat less in studies that were rated as poor quality and overall, again, we see a reduction of about 1% in A1c. There was…in terms of pooling the studies there was significant heterogeneity.

Next. This is looking at studies with pioglitazone whether or not there was pioglitazone compared to monotherapy or pioglitazone in a context of combined therapy in both cases placebo-controlled and, I think, again we can see the magnitude of the effect here is around 1%, maybe somewhat less when you call out combined therapy among…

Next. Basically this is a…people referred to the actual report. This is just the detailed data that was presented in summary on the previous slide.

Next. With respect to rosiglitazone and placebo-controlled trials there were 21 trials, again, looking at the pool effects stratified by quality of study. The magnitude of reduction compared to placebo in A1c is about 1%. It is statistically significant and again there is significant heterogeneity across studies.

Next. Some more slides here for rosiglitazone with respect to, again, monotherapy, placebo-controlled trials and combined therapy placebo-controlled trials and, again, we see about a 1% reduction in A1c…in both…actually across all the strata we're looking there…at all studies monotherapy or combined therapy.

Next. And this is a summary slide of the same information just with the detail that's available in the report.

Next. With respect to indirect comparisons of pioglitazone and rosiglitazone first with…on impact on A1c we can see when looking at all studies…actually when you look at all of this data the point estimates across the strata of good fair quality studies monotherapy combined and so forth are…indicate small differences and the confidence interval in all cases across this one. So there is…even with indirect comparisons there appears to be no difference in terms of the impact on A1c.

Next. For…going on for…oh, this is just a summary in terms of the question fair quality evidence and no significant difference in outcomes of A1c, which is what we saw. Moving on to key question two for patients with type 2 diabetes do glitazones differ in the ability to prevent the macrovascular and microvascular complications of diabetes? First when used as monotherapy and second when added to or substituted for other oral hypoglycemic agents.

Next. There are two fair quality randomized controlled studies that examine cardiovascular outcomes in patients with type 2 diabetes. The one study in 2005 by

Wang, which was rosiglitazone versus placebo, 41% of people included in this were on combination therapy. Presumably other people were just on single therapy and outcome of recent percutaneous coronary intervention and there was…boy…thank you. Six months…at six months there was a decrease in coronary events, which reached a statistical significance and an increase in HDL. That would be in the group treated with rosiglitazone. The second study looked at pioglitazone versus placebo and in this case virtually all the people were on combination therapy. Outcome of macrovascular disease at 34-1/2 months there was…with respect to…I think it was coronary outcomes. I'm not familiar with her…I know in the report it's got…I'm not sure what HR stands for. Excuse me?

[inaudible]

Dan Lessler: Thank you. In the composite…the deposit end point was on cardiovascular outcomes and mortality and there was no effect.

Next. For patients with type 2 diabetes do glitazones differ in the ability to prevent macrovascular and microvascular complications with diabetes with respect to microvascular outcomes there are no data. With respect to macrovascular outcomes there's one study with positive effects with rosiglitazone in one study and positive effects on secondary end points with pioglitazone and I believe that one of the things that's not…in terms of the previous slide…can we just go back to the previous slide? I believe just to be clear this slide is pointing with respect to pioglitazone has to do with the composite end point, which was the primary end point of the study. There was no effect but when you looked at other secondary end points that was an effect. So if you can go to the next slide…that's what the second here under microvascular outcomes with respect to pioglitazone that's what it is referring to just to be clear.

Next. Key question number three for patients with pre-diabetes or metabolic syndrome, do glitazones differ from one another or from placebo in improving weight control when used as monotherapy or when added or substituted for other oral hypoglycemic agents?

Next slide. Weight or BMI was measured in four fair quality studies of patients with pre-diabetes or metabolic syndrome. There were two head-to-head studies and…with respect to weight and…I apologize…I'm…right. But this weight gain…right? They both were associated with weight gain of 1.2 kg in the case of pioglitazone 1.5 in rosiglitazone those in each was…I guess…the differences…is it the difference in here? Could someone remind me? Yeah, it is the difference. And then a second study where…it was…again, I'm going to have…if somebody could look. I'm having trouble just interpreting the abbreviation on the slide. P not reported, thank you. Then with respect to pioglitazone with sulfonylurea, pioglitazone with metformin greater than 10 metformin alone. It looks like in terms of weight gain or sulfonylurea. Is that correct? Yeah. And we don't have…there's nothing there in terms of statistical significance. Then with respect to rosiglitazone it was equal to placebo for weight and waist circumference. So one study showing no real difference.

Next. For patients with pre-diabetes or metabolic syndrome, do glitazones differ from one another or from placebo in improving weight control? Head-to-head increase…do you see an increase in weight both pioglitazone and rosiglitazone weight increased with both drugs and placebo to a similar degree insufficient on comparative effect on weight. So we see some modest weight gain with them and we can't really comment definitively…comparatively.

Next. Weight or…question four…for patients with pre-diabetes or metabolic syndrome do glitazones differ from one another or from placebo in delaying the occurrence of clinical diabetes? Two studies examined the effects of glitazones on incidence of type 2 diabetes in pre-diabetes or metabolic syndrome. One study was of poor quality. Pioglitazone versus monotherapy three years…boy, I'm going to need help interpreting the slide on this having read the full…right…with 172 patients progressions in type 2 controlled… okay…controls the divided…developed diabetes compared to 2% and 1% of…okay. Thanks. Thanks. So with respect to the question of with pre-diabetes or metabolic syndrome do glitazones differ from one another and there is insufficient evidence on comparative effectiveness.

Next. This question for patients with pre-diabetes or metabolic syndrome is the use of different glitazones associated with reversal…slower progression of cardiac risk facts including [inaudible], central obesity, elevated blood pressure and basically with respect to this question there was insufficient data…no data on blood pressure with respect to weight central obesity there was sparse data. We've already mentioned that we know both increase weight and with respect to lipids there was one head-to-head trial with improved LDL, total cholesterol and triglycerides in the pioglitazone versus the rosiglitazone and mixed effects in two placebo-controlled trials.

Next. For key question six for patients with type 2 diabetes, pre-diabetes or metabolic syndrome, do glitazones differ in safety or adverse effects either when used as monotherapy or when added to or substituted for other oral hypoglycemic agents?

Move on. There are three head-to-head trials – Derosa- 2004 type 2 and metabolic syndrome with glimepiride adverse events 6.7% in the pioglitazone, 11.9% reported in the rosiglitazone, none serious. No mention of heart failure. There was an increase in transaminase greater than 1.5 times normal in…I'm not sure what ULN is referring to, but it looks like…oh, upper limits of normal in one patient with pioglitazone and two with rosiglitazone. In another study in 2005 Goldberg there was no difference in terms of LFT abnormalities, hypoglycemic events, edema, and there was no data that was reported on…and no data not reported…okay. Withdrawals pioglitazone 19%, rosiglitazone 22%. Withdrawals due to adverse events were 2.7% for both drugs. And the final study in which adverse events were not reported in the study.

Next. Withdrawals in placebo-controlled trials – overall withdrawal rates have ranged from 7% to 33% in treatment versus those treated with placebo for both pioglitazone and rosiglitazone. Withdrawals due to adverse events treatment was

equal to placebo in most trials for both drugs and the risk differences versus placebo were…looks like they were not significant in pioglitazone and were…did reach significance in rosiglitazone. That would be…somebody want to help me interpret the minus 2% here? Okay. Let's go on to the next one.

Weight change in type 2 diabetes head-to-head trials…in one study by Derosa in 2004 no significant difference between groups. Both showed an increase in some increase in weight. In a second trial again no significance…it appears that there was a weight gain in both groups. The difference was not significant and same with the third trial.

Next. And this is a summary of that data.

Next slide. Peripheral edema in placebo-controlled trials. The incidence range from 0% to 27%. Both pioglitazone and rosiglitazone appear to have more edema associated with them than placebo. Pooled risk difference was 4% for pioglitazone and 8% for rosiglitazone.

Next. Macular edema there is a manufacturer's issued warning in December of 2005 regarding reports of macular edema in patients taking rosiglitazone and the OHSU review found no cases in the literature.

Hypoglycemic episodes – the incidents range from 5.2% to 11.9% pool risk differences stratified by medication where 2% in the pioglitazone and 3% in the rosiglitazone.

Next. With respect to liver function tests, elevations of ALT greater than 3 compared to normal are rare and either 0 or less than 1% are reported in placebo-controlled trials.

Next. Heart failure – pioglitazone two placebo-controlled trials with insulin…the incidents of heart failure was 12% and 1% of the latter. There was no significant difference versus placebo. 24-week post-marketing study in patients with heart failure, hospitalization reported in 9.9% of patients taking pioglitazone versus 4.7% taking glyburide. The effect appears to be greater in patients taking insulin and there is no difference in cardiovascular mortality.

Next. Observational studies comparing the two medications – 11 studies adverse events were the primary outcome measure in 5. Few studies followed patients more than 6 to 12 months. Certainly not longer than efficacy trials. Peripheral edema occurred at similar rates. The incidents of heart failure…with respect to the incidents of heart failure a retrospective cohort study done with claims data with up to 40 months of follow up – pioglitazone had a hazard ratio of 1.92 that was significant. Rosiglitazone had a hazard ratio of 2.27, also significant and the between group did not appear to…that is I believe that was pioglitazone versus rosiglitazone did not reach statistical significance. And no significant difference in weight gain across 7 studies.

Next. So with respect to adverse events summary head-to-head and placebo-controlled trials provide good evidence that the glitazones are similar for overall withdrawal and withdrawals due to adverse events. Both glitazones were associated with increased weight. No significant difference between the medicines. The incidents of other specific adverse events similar in placebo-controlled trials between pioglitazone and rosiglitazone with respect to edema and hypoglycemia and greater than placebo and the quality of reporting of adverse events in trials was fair to poor.

Next. Key 7 – how do glitazones compare to sulfonylureas in serious hypoglycemic events, functional status and quality of life?

Next. Pioglitazone there is fair evidence of less hypoglycemia than sulfonylureas in the case of monotherapy. In rosiglitazone there is insufficient evidence for monotherapy. Rosiglitazone and sulfonylurea may produce hypoglycemia and there are three studies to this effect. And with respect to comparing pioglitazone and rosiglitazone there is…compared to sulfonylureas with respect to hypoglycemia there is insufficient data—there's no data on qualify of life or functional status.

Are there subgroups of patients based on demographics, concomitant medications, co morbidities or a history of hypoglycemic episodes for which one glitazones is more effective or associated with fewer adverse effects?

With respect to demographic subgroups there is poor to fair quality evidence that glitazones have similar effects in different racial and ethnic minorities. No direct comparative data. Comorbidity subgroups – insufficient data on renal insufficiency, obesity and cardiovascular disease to make a comparison and no studies examined the effect of concomitant medications or history of hypoglycemia.

And that's the presentation from OHSU. I think what I will do is just maybe open it up for comment or clarification if there is anything I might have misinterpreted in terms of the slides. If we went through looking at abbreviations or for other observations from committee members. Janet?

Janet Kelly: Janet Kelly. Just to kind of give you my…the way I think this…these agents very, very similar. They don't really make any particular advantage one way or the other on any of those and in practice that's what I see. The other thing I see in practice is that most of the time I spend time trying to get people off of these agents because of the weight gain, because of the fluid, and especially in a cardiac population. That's probably what the majority of my referrals are is someone who has been in the hospital with, you know, cardiac disease on this agent because there is this feeling that we want to use an oral agent and then it is getting them off of it and putting them on insulin at that point. That's where I see so much of these people who use these drugs because they want to avoid using insulin or having to do injections and so these get put on top and I think the biggest thing is, "Are they really appropriate for those indications?" That's probably not what we're talking

about today, but in my mind are the same. You could kind of group them together. It's just the issue of, "Should they really be using those agents?"

Vyn Reese: Hi, this is Dr. Reese. I don't use these agents much clinically anymore and I don't see where they fit actually. I mean we have sulfonylureas, we have metformin, I've had bad experience with them in the past in elderly patients developing digestive heart failure. A lot of times diabetics have had silent microinfarctions and you don't know their left ventricular function and you put somebody on one of these and you can find out real quick the ones that don't have good LD function. I asked one of my endocrinologist friends to review, you know, where he thought they were used and he said he doesn't use them much either, you know, because…he said, "What I use them for is in the patient who is needle phobic. They're already maxed out in their sulfonylurea and their metformin and you add these because it helps a little bit, but it's probably not going to [inaudible] insulin anyway." So when I'm maxed out with somebody who is on sulfonylurea and metformin I go to insulin. I don't use these. He said he uses them occasionally in patients who are elderly before you can't use metformin because you have, you know, [inaudible] sufficiency where you get hypoglycemia even on a fairly small dose of sulfonylureas. You don't use a little dose of one of these drugs and hope they don't have heart failure. And then he also uses them in patients with metabolic syndrome and severe hypertriglyceridemia where they may help your triglycerides a little bit more if they are maxed out in all the other drugs we have for triglycerides and that's about it. So I think these drugs are extensive. They are niche drugs for patients who fail other drugs or can't, you know, adequately controlled in other drugs and I don't see why we should have them on the formulary.

Dan Lessler: Let's stop here because we're doing this a little bit differently this time since I did the presentation I would appreciate the input. We'll come back to the P&T committee members and I do want to open it up for stakeholder comment. First is Dr. Horner from GlaxoSmithKline.

Neilann Horner: [inaudible]. Thank you. I guess it helps to hold that, doesn't it? Another paper…in similar design looking at the metformin combination with the Avandia. So I think the role is as a second agent in folks and it's to be used early on rather than end stage, last ditch effort, [inaudible] to avoid sulfonylurea. That was never the intension, but rather early on based on molecular work associated with the permitted component.

I will remind that both TZDs on the market only have an FDA indication for treating type 2 diabetes. You have four out of eight questions in the report that [inaudible] for you that are in metabolic syndrome in pre-diabetes and the drugs are not indicated in that class. The report has direct quotes and I'll just paraphrase here. I have them written before me, however they are basically finding no difference in microvascular or microvascular with microvascular data lacking and no difference in cardiovascular risk factors found by the report. And that's on page 56 in the summary. Avandia specifically is the only TZD with a triple indication. That is sulfonylurea, [inaudible] formula, plus TZD. You may be aware that the American Association of Clinical Endocrinologists recommends combination therapy. That is more than one oral agent be initiated in the range of A1c,

gly[inaudible] hemoglobin 6.5% to 8.5% and they are recommending in their list of five drugs TZD, metformin and SU and options to do that.

Avandia and metformin and Avandia and Amaryl are combination products now available as of April. The Amaryl combination is available with a [inaudible] improvement, statistically significant demonstrated versus the two separate pieces taken in equal doses. And finally, Avandia does avoid the [inaudible], which is thought to be a fairly high traffic. The clinical significance of that is unclear; however, with the standard of care being [inaudible] in the background, as well as oral contraceptives with estrogen in a polypharmacy cloud, which was never clearly tested when you look at interaction studies. You never have six agents on you—the two agents of interest. It might be important in clinical practice. And with that I would like to recommend that Avandia is available on the formulary Washington State. And I'll take questions if I can help any further.

Dan Lessler: Thank you. No questions. Next is Steven Stein with Takeda Pharmaceuticals.

Steven Stein: Good morning. My name is Steven Stein and I'm the Regional Scientific Manager with Takeda Pharmaceuticals in the State of Washington and I would like to discuss Actos, one of the two thiazolidinedione. The generic name is pioglitazone. I confer with Dr. Horner as far as these drugs are indicated for insulin resistance. It is really important to remember that for type 2 diabetes. It's true that no TZD is indicated for cardio vascular. I'd like to point to a study that was announced last year, the American…the Drug [inaudible] Association studied diabetes called Proactiv. The practice study was published in [inaudible] and it was a cardiovascular outcome study that investigated the ability to Actos to prevent secondary macrovascular events in patients with type 2 diabetes. Patients were randomized to receive Actos or placebo in addition to standard of care including other anti-diabetic and cardiovascular therapy. In this study the primary end point of seven different macrovascular events of varying clinical importance was reduced down significantly by 10%. However, the pre-defined main secondary end point consisting of all causes of mortality, heart attack and stroke was significantly reduced by 16% in the pioglitazone group.

Overall safety and tolerability in Proactiv was consistent with no adverse events associated with Actos. Compared with placebo more patients in the Actos group were hospitalized with heart failure, 4% and 6% respectively, however, it is important that the heart failure mortality rate did not differ between the treatment groups.

A subgroup analysis of the Proactiv study, which was presented at the American Heart Association meeting last year included patients in the Proactiv study who had a myocardial infarctions prior to enrolling in the study. There was a statistically significant 28% reduction in the recurrence of fatal and non-fatal myocardial infarctions and a 37% reduction in episodes of acute coronary syndrome. There was a 19% risk reduction in the cardio composite end points of non-fatal myocardial infarction, coronary revascularization, acute coronary syndrome and cardiac death, which was statistical significant. Overall safety and tolerability was consistent with the whole Proactiv cohort.

I would also like to address question number 5 from the Oregon EPC where it says there is insufficient data for the blood pressure. If you read the Proactiv publication in [inaudible] you will see that the patients that were on pioglitazone actually had a significantly significant decrease in blood pressure. And this study went over three years. So definitely TZDs are showing a certain effect on blood pressure and the mechanism is still being determined.

As far as the metabolism of pioglitazone, all of these patients over 5,000 were randomized into pio placebo. 2,500 or so in the pioglitazone arm were on multi-therapy statins, other anti-diabetic agents and no adverse events as far as liver function tests were observed. I thank you for your time.

Dan Lessler: Thank you. Any questions from P&T Committee? Okay. That's all I have in terms of people signed up for stakeholder input. Did I miss anybody? Okay. Do you have a comment, Jeff?

Jeff Graham: Yeah, this is Jeff Graham. You may be wondering why we chose this class to be reviewed. The participating organizations when they discussed classes to be reviewed there were several members who had attended recent meetings particularly internal medicine organizations stated that this was a drug that was going to be used in the increase because of what was being said at that meeting and that's why we added several of these, you know, metabolic syndrome and weight gain issues and so forth because of the information that was coming out to our members. So I think we still are pretty interested in it being a drug on our preferred drug list or this class anyway just so we can kind of be able to monitor it and so forth.

Dan Lessler: Okay. Thanks. So are there any other comments or observations from committee members at this point? Siri?

Siri Childs: This is Siri Childs. Is it working? I also wanted to add to Jeff's statement that one of the purposes of the review was to see what these agents placed in therapy compared to metformin and sulfonylureas was. So it was kind of like there were two issues that they wanted to address.

Dan Lessler: Thanks. So what I've heard so far just in terms of comments from P&T Committee Members is really that…I think both members have spoken so far is that they see a very limited role for the medications in terms of where actually is, you know, appropriate in clinical practice and that from what we've seen in terms of the data presented on the two medications that they are pretty much equivalent with respect to effectiveness and safety. Does anybody want to comment more beyond that? Carol?

Carol Cordy: I know our personal [inaudible] aren't really…shouldn't really be a factor here I don't think. But also reminding that I actually find these drugs quite helpful in a number of particularly younger patients. So just to balance that. I think they do have a place. The other thing is that I think when we aren't covering off label

uses…is that right? So we wouldn't include the metabolic syndrome or prevention of diabetes. Is that right?

Dan Lessler: Yeah.

Carol Cordy: Do you just want me to make the motion?

Dan Lessler: Yes. Yes?

Alvin Goo: Hi, it's Alvin. I agree that the evidence sort of supports the possible benefit of using it for glucose intolerance and the development of…for further progression in diabetes and that as far as the ability to reduce A1c is very minimal. Whether it will reduce cardiovascular disease is still to be decided with better studies. The Proactiv study that was mentioned is interesting in that the primary event or primary outcomes were not significant, but the secondary outcomes, which were similar showed some statistical significance but again, you know, the secondary outcomes so we don't know what to make of that. So I think a lot of this still has to be developed as the new studies come out and although the incidents of CHF(?) deaths are not statistically significant it is kind of concerning that there is some similar to 3% absolute differences between placebo in the active groups and development CHF. So that benefit may overcome the actual benefit of cardiovascular disease. So I think…there seems to be a lot of studies to help us decide where the role of these thiazolidinediones are in diabetes, but I agree that it is sort of not well defined yet at this point.

Vyn Reese: This is Dr. Reese. I agree. I think the benefits for these drugs are…I don't think the data is out. They don't do much for diabetes per se. They don't drop the hemoglobin A1c much and there is talk that they much help all sorts of other issues, which we have other drugs for—statins and for lipids and fiber aids and other things for. So it's like…it's like they are struggling to find an indication right now and I don't see the data is there that they are better than drugs we have already for those indications or that they really are something that we should add because of the secondary indications when they don't really do much for diabetes. And so, you know, I think we need to have access to them and there are patients that need them, but I think it is [inaudible] small group and they are very expensive. They are budget busters as far as how much they cost. There are cheaper drugs that work better and the insulin is…it clearly works better than they do. So I don't see a place for them with the current data we have I don't think there's evidence that says that they are better than drugs we already have and they may be better in some other areas, but that isn't it. I think we should reserve adding them at this point and we should look at it again in a year and see if there is more data saying we need them for some reason.

Dan Lessler: Bob?

Bob Bray: This is Bob Bray. I don't disagree with the comments that are made, but I'm just really uncomfortable with a class of drugs saying that because they're not clearly better than others that we should not have them on the PDL. So I guess my thought would be that many of the things that have been raised and discussed might be

more appropriate for the DUR(?) as far as how the use of the drugs would be possibly restricted than to just eliminate them from the PDL entirely.

Dan Lessler: Siri?

Siri Childs: We can always put these on an EPA criteria. They can be on a preferred drug list. You can give us the recommendation based on their comparative safety and efficacy. We can select a preferred drug in this drug class, have it available, but it would be…it could be on an EPA for a particular use, second line use or whatever you would like to recommend.

Dan Lessler: Yeah?

Angel Ballasiotes: Um, Angel Ballasiotes. Siri, you mentioned something with regards to monitoring them. Is it just the use of them? Are you going to be monitoring anything else on these medications?

Siri Childs: I'm not sure what you mean by monitoring?

Angel Ballasiotes: I think you mentioned it…you were going to be monitoring these drugs on the formulary. That's what I thought I heard you say. I may be mistaken.

Siri Childs: I think the clarifying statement is that we can handle this any way you give us the recommendation. We can have it as on the preferred drug list, we can select a preferred drug from the two if that's your recommendation and we can put qualifying criteria for the appropriate use if you ask us to do that.

Dan Lessler: So there could be criteria applied even if the drug is on the preferred drug list? Donna, can I ask you a question then in terms of uniform medical? Just to, again, I don't know if you or Nancy would be appropriate to answer. Just what are the, you know, one thought that has arisen is just not recommend…recommending that these drugs not be added to the preferred drug list at this point. I'm just wondering what the implications of that would be from…for the other agencies such as uniform medical?

Donna Sullivan: This is Donna Sullivan. If you did not add them to the Washington preferred drug list then we would treat this class as they are treated with the express scripts, national preferred formulary. So they would still be available to our enrollees, they just wouldn't have the interchange or the DAW.

Dan Lessler: And does it affect the [inaudible] of this medicine?

Donna Sullivan: I believe Avandia and their family of products are our preferred drug right now and Actos would be non-preferred. So if you did not add them to the PDL at this time that wouldn't affect that at all.

Dan Lessler: [inaudible] about it for L&I or others whether there are any implications one way or another?

Donna Sullivan: There is no implication.

Dan Lessler: Thanks. Are there other comments? Carol?

Carol Cordy: I just have a question. What would we be trying to do by not including them on the preferred drug list or making it an EPA drug? You know, as a group, what is the motivation or the point of not including them?

Janet Kelly: Janet Kelly. The [inaudible] that I had is that I think there are patients that they are indicated for and that they are beneficial. To get a 1% decrease in the hemoglobin A1c is not a huge impact, but that's typically what we see with oral medications. So I think that it's…for those patients my big concern is that I get patients that have known heart failure that are on these agents and I think that we need to put…if there's a way that you can put that, you know, put that as a prior, you know, is there a history of heart failure? And that pops them out of the system. That would make me much happier. But as far as which agent they get I really don't care. They are equivalent in my mind.

Carol Cordy: That would be similar I would think to tons of other medications that…well for say for PPIs whereas if you have a history of ulcers that's a relative contraindication. So would it be similar to that for these…for congestive heart failure?

Siri Childs: It wouldn't be for the PPI, it would be for the…

Carol Cordy: [inaudible]

Siri Childs: Yes.

Dan Lessler: I see the risks for these drugs and they will be used as [inaudible] agents as the initial drug and I've seen this already in clinical practice. Usually the first drugs people go to and if you start adding drugs for pre-diabetes like metformin has been shown to be effective too you can start treating people before they have the disease yet and it can be incredibly expensive and the benefit for that is pretty small. And I think that we need to look at how these drugs are going to be used. They are going to be marked as [inaudible], but you know that this is a drug that's a patented drug…these drugs are both patented. They are going to be marketed heavily and doctors will be encouraged to start them first, which I think is a major mistake for the state.

Jeff Graham: This is Jeff Graham. Actually, Medicaid already has to cover these drugs. So they are available to patients who are on Medicaid. Medicaid has to cover these drugs and so they are already available for them. I don't know if you have any…any EPAs on those right now. So I mean, I think, that you might even do much better by adding a class to the PDL and working with Medicaid to make sure it's given to the right patient.

Duane Thurman: This is Duane Thurman and the pharmacists cut me off if I'm incorrect here, I think Carol's question, you know, what are you trying to accomplish by not putting these on the PDL is interesting because what we're trying to do is we already covered

these drugs and we're paying for these drugs and the purpose of your evidenced based review is to look at the, you know, is there some difference here to give us the best shot at purchasing from an evidenced-based standard? In terms of the discussion about how these drugs are prescribed or whatever, that could be something you bring up in the DUR portion, the utilization part and so we're sort of discussion the utilization side when what we're also looking to as the P&T Committee, we're looking for help in our purchasing. We've got to buy these drugs anyway. If you find no differences then, you know, our next steps are to do it on the basis of freebase or, you know, then it costs the state, which is not a part of your discussion, but is our internal mechanism for trying to purchase the most effective way. But as far as follow up there are a lot of options that could be done.

Dan Lessler: Thanks, Duane, for that clarification. Are there any other comments from P&T members at this point? It sounds like potentially there might be sort of two schools of thought here pending. One is to have a motion that…don't add it at this point and then the other would be a motion that reflected the outcome of the evidenced-based review and I guess Janet and then the two of you have sort of spoken to the concerns about the medicine, maybe concerns about actually putting them on the PDL. It might be…if you wanted to move forward with a motion like that it might be just to sort of take a look at that first if…and then go from there because obviously if a motion like that were to pass then, you know, we wouldn't have to consider alternative approaches. I don't know where you're at having heard the discussion so far. I guess my question is, "Do either of you want to make a motion at this point?"

Janet Kelly: I can try. Janet Kelly. After considering the evidence of safety, efficacy and special populations for the treatment of type 2 diabetes, I move that pioglitazone and rosiglitazone are safe and efficacious options as second line therapy. No single thiazolidinedione medication is associated with fewer adverse effects in special populations. They can be subject to therapeutic interchange in the Washington preferred drug list. And I think just maybe…I don't know if that…putting it as a second line agent makes it so that we can do that piece.

Vyn Reese: This is Dr. Reese. I don't know whether you can monitor or whether they can try it on sulfonylureas or metformin first and whether you have that monitoring capability and that would be what second line agent meant. I wouldn't have a problem if that…if it was worded in that regard and the state has the ability to monitor that.

Siri Childs: Again, that would be EPA…this is Siri Childs. Again, for Washington Medicaid that would be part of the EPA criteria that we would establish.

Donna Sullivan: And this is Donna Sullivan. For uniform medical plan what we could do is implement some sort of step therapy where we can actually look at their claims history whether they process a claim for this, if they have a sulfonylurea or metformin in their history then the claim would go through automatically, if not it would reject with a prior authorization required and then we would just handle it like we do all other prior authorizations.

Dan Lessler: Okay. Is there any other comment? So Janet do you want to maybe read this and make it…put it forward formally as a motion and see what…

Janet Kelly: After considering the evidence of safety, efficacy and special populations for the treatment of type 2 diabetes, I move that rosiglitazone and pioglitazone…it's actually the other way around. It doesn't matter. Are safe and efficacious options as second line therapy. No single thiazolidinedione is associated with fewer adverse events in special populations. Thiazolidinedione can be subject to therapeutic interchange in the Washington preferred drug list.

Dan Lessler: That's the motion on the table. Is there a second?

Jason Iltz: I'll second.

Dan Lessler: Okay. Seconded. Any other discussion? All right. All those in favor, please say I.

Group: I.

Dan Lessler: I. Opposed, same sign? All right.

Dan Lessler: Jason. We had multiple. And so the motion carries. Thank you. So at this point, Jeff, I think we finished a bit early. We have a busy afternoon schedule with people who are actually scheduled and need to be here to join us. So we can't get started early on that agenda. So I think we're actually going to adjourn.

Woman: You are ready to go for lunch.

Dan Lessler: So I think we are going to enjoy a long lunch. Thanks. We'll reconvene at 1:00.

…presentation and Marian McDonagh is on the line, I believe, from OHSU. So Marian, are you there?

Marian McDonagh: Yes, I am.

Dan Lessler: Great. And so I believe we've had a chance to sort of communicate with you about some of the questions that were raised and I was just going to allow you to grab…take a moment and respond to those questions if you would.

Marian McDonagh: Sure. What I have…I had a telephone conversation and I never did get a follow up letter or list of the citations so I can address the comments that were directed at things that I particularly said. I can't really address anything additional to that. Okay?

Dan Lessler: That's fine.

Marian McDonagh: Okay. So I think the first comment was that I was asked the question about hospitalization rates and I did answer that incorrectly. They did in fact look at hospitalization rates and I'm sure many of you are aware of that. The analysis that was done in the publication was to look at a group-wide comparison. So

comparing olanzapine to all of the other drugs as a the group. And there was a significant…statistically significant lower rate of hospitalizations in the olanzapine group. Looking at doing pair-wise comparisons here at our ETC I can give you a little bit more information on looking at which of those drugs might have a higher rate than olanzapine. It looks like the differences were with quetiapine and ziprasidone and of course ziprasidone having a much smaller number of patients than the other groups. So that could change if there was a larger number of patients. Confidence intervals were fairly wide on all of these. The confidence intervals for olanzapine versus risperidone and olanzapine versus quetiapine crossed the non-significant point of zero. So I thought you might want a little more information than was in the paper on that one.

The other point that was raised was that I was asked about the exclusions that were in the study [inaudible] and actually the one thing that in particular I didn't point out was that there were some exclusions for cardiac abnormalities and in particular both [inaudible] for 2Tc problems. So there were several exclusions relating to QTC, but in addition to those there was also exclusions of patients who had had a recent MI, anything in the last six months. And then patients who had uncompensated heart failure, complete left [inaudible]. I can't talk, sorry, bundle branch walk(?) and first [inaudible] heart block. So those are the other things that I had incorrectly stated in the last…when I was talking to you last.

Dan Lessler: Okay. Thanks.

Marian McDonagh: I don't know if there are other questions about either those issues or the other issues that were raised.

Dan Lessler: Right. With you on the phone I was just going to ask that of the committee members. Whether members of the committee had any questions or want any points of clarification relevant to Mary's presentation the last time we met on antipsychotic? I also want to welcome Dr. Sharon Farmer who is back, again, joining us as a consultant—expert consultant to help us with our decision-making. Dr. Farmer is available, I think, to respond to questions and provide her insights and, actually, Dr. Farmer, I didn't know whether you might have any questions for Mary, as well in terms of the presentation from OHSU last time, as well?

Sharon Farmer: No.

Dan Lessler: No, okay. So I think Mary that is very helpful. Actually, I think…I appreciate the clarifications and I think we can let you go at this point. Thanks a lot.

Marian McDonagh: Okay. All right. Thank you.

Dan Lessler: Yeah, bye, bye.

Marian McDonagh: Bye.

Dan Lessler: Okay. So next we were going to open it up here for additional stakeholder input and last time we had the opportunity to hear from a number of different people and

we definitely appreciate the input from the stakeholders, but I do want to ask and did stipulate the last time that we met that if you spoke the last time we ask that you not speak again this time unless you really have something specific in addition to say to what you said last time…what you might have brought up last time. So I really don't want to re-hash old material here. I would ask people to respect that request, as well as I just want to remind people that we'll be asking folks to limit their comments to three minutes and please identify what organization you are representing if you are representing an organization and also if you're here under any financial sponsorship from any entity, please let us know. So with that as background I have a list of people who have signed up and does everybody…is there anybody…let me ask…is there anybody who has not signed up that…there are these sign up sheets just to make sure that…and people are welcome to still sign up. I just want to make sure we've got…okay. Did you…okay…I'm sorry, I forgot you're name. I apologize. Did you want to add your name to the list? Okay, great. Thanks. Is there anybody else who might not have signed up who would like to speak? All right. So we'll begin then and the first person on the first list is Caroline Wise.

Caroline Wise: Can you hear me okay? Okay. I represent Rose House. I'm the Education Coordinator there and we're a rehabilitation organization that works mostly with people with chronic and severe mental illnesses and we are looking at moving people beyond maintenance into thriving and we really have seen some success with that. The majority of the people that are in our program use atypicals and we have a recent graduate from…got their master's in business and we have several in graduate school that have a quality of life they would have never had without the use of atypicals. We have many that are employed full-time and just wanted to say that we want to keep seeing people thrive and keep the access to atypicals open. Thank you.

Dan Lessler: Thank you. Next is Chief Larry Saunders.

Larry Saunders: Hi. My name is Larry Saunders. I'm the Police Chief in the City of Lakewood. We have the honor of hosting the largest mental hospital west of the Mississippi in Lakewood. We have a wonderful partnership with them. In terms of qualification I also am a former board member of Greater Lakes Mental Health Regional Service and currently serve on their Assessment Committee. So I hope I bring their perspective as well as mine. We believe in the theory that is both better therapy and economically more responsible that [inaudible] institutionalized and have mentally ill sustained in the community. The challenge we've had in Lakewood is while the decision for the institutionalization to be made they haven't necessarily followed with greater capacity to maintain good behavior in treatment for outreach organizations like Greater Lakes Mental Health. Our concern is that an improper decision on restricting…potentially restricting medication might compound that as well. We believe that it is essential that doctors be allowed to make the decisions that are necessary to both improve the likelihood that the individual can integrate well into the community and it's my [inaudible] appreciation based on counseling and coaching from Greater Lakes Mental Health that the atypical treatments, medication will do that whereas the traditional treatments make those behaviors more problematic and that the patients are less likely to take the typical medications

than they are the atypicals. So I would encourage the committee to make the decision to allow the doctors freedom in assigning the medication that is most likely to sustain the individual successfully in the community. I would just point to the fact that when…from a law enforcement perspective I can speak with a little bit more precision. In most cases our interactions with mentally ill are based on someone who has stopped taking meds or the meds are not working. Those interactions can be extreme. Even when they are not extreme they generally end up in jail, incarceration and that's both much more expensive to taxpayers and much less productive to the mentally ill. So we beg your support in allowing doctors full freedom in assigning medications that work in both negative and positive of behaviors. Thank you.

Dan Lessler: Thank you. Next is Peter Lukevich.

Peter Lukevich: Mr. Chairman, I appreciate your caution to begin the meeting with. I won't be testifying, but I would like to present the information on behalf of Chief Deputy Karen Daniels of the Thurston County Jail as opposed to my last presentation. Again, a letter addressed to Mr. Thurman that will reach his desk in short order, I hope. In summary, Mr. Chairman, because I know that in the interest of time you want to keep moving forward. Sighting her 25 years of experience in corrections, as well as 15 years with Thurston County, Chief Daniels notes that based on her experiences and knowledge she encourages the pharmacy and therapeutics committee to recommend that all medications be available to doctors at all times so that they can properly care for those clients that find themselves into the community-based treatment facilities, as well as to her jail. Our doctors cannot effectively treat these clients if the medications are not readily available. Many lives are at risk when they are confronted with mentally ill offenders that are not being treated with their medications. Please do not limit access to the appropriate and necessary medications. The lives of citizens, the mentally ill, and law enforcement are at stake.

And then finally from the position of the Washington State Partners in Crisis, which is the organization that I represent that coalition of law enforcement and criminal justice stakeholders urges you to make all of the atypicals available as first line agents and to not permit the therapeutic interchange of those agents that are found on the preferred drug list as first line agents. We feel that the evidence in this particular case that's been reviewed is sufficient to reach that conclusion and we would encourage you to adopt that as your outcome and recommendation today. Thank you.

Dan Lessler: Thank you. Next is Mr. Barry Adkins.

Barry Adkins: Thank you Mr. Chairman. My name is Barry Adkins and I'm here to represent the National Asian Pacific Center on Aging. Before I was a policy analyst there I worked in several mental health clinics and drug abuse clinics and what I would like to present to you today is that our organization urges this committee to recommend that all atypical antipsychotics be included on the preferred drug list especially in Washington state. The Asian and Pacific Islander or API communities face linguistic and cultural barriers in communicating with their

mental health issues and clinicians. There remains a great stigma in our API communities or acknowledge or address mental health issues that may call for treatment with atypical antipsychotics. It is central that the API community have access to all atypical antipsychotics as the API community has not been fully studied in clinical trials that we are aware of. Clinical experience by prescribers is the only way we have to know which drugs work best in our populations. Culturally there is a great [inaudible] in understanding the use of mental health drugs in the API community and it is imperative that the API community have access to all forms of treatments and medications, including all atypical antipsychotics. As many individuals in the API community were born in Asia or Pacific Islander countries it is important to understand that their exposure to mental health services has been severely limited as they have come to the United States. We respectively request that the committee recommend that all atypical antipsychotics be included in the states PDL. Thank you.

Dan Lessler: Thank you very much. Next is Mr. Andrew Davis.

Andrew Davis: Hello. I did speak at the last session. So I'll just briefly say that I attribute the fact that I'm employed today and paying taxes to the fact that my doctor had a wide variety of atypical antipsychotics to choose from. That selection was necessary in my case. Thanks.

Dan Lessler: Thanks. Marie Jubie.

Marie Jubie: Yes. My name is Marie Jubie and I'm involved in various things, but I want to begin the [inaudible] bipolar disorder and when you get the right mixture of meds you'll find any way to keep it because this just…we live in a living hell and these medicines help. So especially somebody who is psychotic and hearing voices. I have a friend that's in the hospital right now because she wasn't taking the proper medication. She heard voices. These voices told her to stab at the wall and get the electric lines out of there because she was being listened to by the whatever and she just, you know, she had the right mix for a long time, but then one of the doctors changed it. We just have to think about the people. That's what we're here for not for whatever or it's too cheap or it's too expensive. And a lot of these medications are dreadfully expensive because I'm not eligible for Medicaid. So I have to pay for them myself, but luckily, luckily I get Medicare Part B and we'll see how long that lasts. But please think about the people before you make these decisions. Thank you.

Dan Lessler: Thank you. Next is Mr. Jeff Hille.

Jeff Hille: Good afternoon. My name is Jeff Hille and I work in the medical division of Eli Lilly & Company. I'd like to begin by thanking Dr. McDonagh although she's not on the phone for her additional clarification from her comments last time. I'd also like to thank this committee for their continued support and dedication for reviewing this class of medications. Today I'd like to provide comment in support of open access of the atypical antipsychotics. As we know, schizophrenia and bipolar disorder are life-long illnesses with potentially devastating consequences for patients, families and communities. It's important to consider that patients with

these disorders are not all the same and have different symptoms, severities and subtypes. Additionally, the medications available to treat these disorders are not all the same and have different receptor affinity profiles and pharmacologic activity. Not all patients will respond the same to a given medication and clinicians treating these disorders must focus on quickly identifying the right medication for the right patient in order to prevent relapse.

Research has shown that relapses are associated with both clinical and economic consequences. Not only is relapse associated with treatment resistance and a longer time to treat than response, it's also associated with increased costs with the average annual cost of treating patients who relapse being three times higher than the cost of treating disabled patients.

The schizophrenic patients, even short gaps of medication coverage, gaps as little as 1 to 10 days have been shown to double the risk of a costly hospitalization. Additionally, interrupted medication use has also been shown to lead to a four-fold increase and the risk of suicide and/or a two-fold increase in the likelihood of having a legal issue. Patients with schizophrenia and bipolar disorder are a vulnerable patient population.

Studies have evaluated the consequences of access restriction in Medicaid programs. The results typically show that while these programs may lead to decreased pharmaceutical expenditures, the pharmacy savings are often offset by increased costs from other health care services such as inpatient stays.

I would like to finish with a quote from Steven Sumeri(?) who is a leading health policy researcher at Harvard Medical School who writes and I quote, "Financial or procedural barriers to medication access should be avoided in the most vulnerable, high risk populations for whom careful selection of medications can prevent severe illness, hospitalizations or death." Again, I would like to thank this committee for its continued dedication to reviewing this class of medication.

Dan Lessler: Thank you. Next is Dr. Stephen Schilt.

Stephen Schilt: I appreciate the opportunity to address the committee on this important matter. I'm a medical director at Comprehensive Mental Health in Tacoma. And as such have a vested interest in ensuring that this high-risk population we serve has access to psychotropic medication that provides most optimal treatment.

Decisions concerning formularies are currently driven by evidence-based medicine. The problem is that in the real world of non-research based clinical settings our use of psychotropic medication is often not directly driven by given diagnosis and further patients seldom well fit the kind of rigid diagnostic criteria used for patient selection in studies required for FDA approval. This reflects a problem since the psychiatric profession often avoids discussing. The fact is that none of our psychiatric diagnoses are indicative or reflected of exactly what is going on in the brain at a neurochemical or cellular level. When we move from somewhat arbitrary symptom-based diagnoses to FDA approval of drugs and for a given narrow diagnosis and finally to the real world of clinical patients there is an extreme

disconnect. This results in much of the psychopharmacology being administered in cases that do not fit FDA diagnostic indications for use. Nowhere in the field of psychiatry is this more evidence than in the use of atypical anti-psychotics. Most of these agents are approved for schizophrenia and bipolar type one and often only [inaudible] within that. But despite the party line that suggests we are diagnostically driven much of the time these agents are used in reality for various target symptoms or combinations of symptoms resulting in the vast majority of use being off labeled.

Various studies, case reports and clinical experience demonstrate that all the atypicals have the potential to impact a wide variety of symptoms including voices, paranoia, good stabilization, mania, depression, anxiety, obsessions, compulsions, stuttering, Tourette's, sleep disturbance, aggression, irritability and probably others.

The atypicals impact a wide variety of neurotransmitter systems that helps account for their ability to impact such varied symptoms. These different…there are differences among them in terms of side effect profile and clinical effects, as well as individual differences that result in some responding to one and not another. With these agents having the potential to dramatically impact such a wide variety of symptoms it is essential that we physicians be given the widest options as we attempt to treat some of the most psychiatrically impaired in our society.

The mental health clinics are under increasing pressure to prevent the need for in-patient treatment. With failure to do so having rather serious financial impact on clinical budgets that are already stretched beyond the limit. It is essential that we have every tool in our psychotropic armor [inaudible] to limit the need for inpatient treatment, which represents a far greater cost than the most expensive medication regime. I strongly recommend that the committee give approval making all antipsychotics equal…equally available without restriction for the treatment of this difficult population. Thank you.

Dan Lessler: Thank you. Next is Mr. Leigh Simmerer.

Leigh Simmerer: Essentially I'll be making the same point that many people have made that it costs a lot more to hospitalize someone than to give them study medications that don't have bad side effects and that they are willing to take. I myself am a bipolar patient. [end of Side A]

[Side B]

Leigh Simmerer: And so I know how much better I felt when I switched over from [inaudible] to Risperdal. For one thing my hands stopped shaking. They started shaking the last couple of years, but it's easier to get people to agree to keep taking their meds if they fit them better and we only find that out by trial an error much of the…

[inaudible] proposed [inaudible] open formulary is what's needed to try to prevent hospitalizations and to prevent jailings of people who may not respond well to jail regimen anyway. So I'm in favor of an open formulary and the doctors have the right to prescribe whichever medication works best. Thank you.

Dan Lessler: Thank you. Next is Larry Cohen.

Larry Cohen: Hi, I'm Larry Cohen. I'm with Washington State University and the Washington Institute for Mental Illness Research and Training. And many of the points that I wanted to make have already been made and I am aware that the mental health taskforce that I also participated on has recommendations that will be presented, as well.

A couple of key things that I wanted to mention. First, it's my personal opinion that all the atypical antipsychotics should be approved medications and I want to further go on to say that these need to be available not just in the mental health community, but in correctional facilities, as well. Continuation of the medication that's gotten well needs to be continued so that we can avoid unnecessary admissions either to inpatient facilities that are medical based or correctional facilities. I think the recommendations that are coming forth from our task force are actually very reasonable and I look forward to those being reviewed and considered by the P&T Committee.

It's important to use whatever is needed to optimize adherence for patients. This is a population that's fairly ill and anything that we can do to get people to [inaudible] to their own devices, continue their medication on an outpatient basis saves us a huge amount of money by reducing hospital days and it's important that we match the drug to the patient.

In a lot of the studies including what I heard reviewed by the Oregon Health Sciences folks when they looked at their evidence-based reviews many of those do not consider in-patient, out-patient drug therapies and other costs associated with behavior health care. They look clearly at a drug compared to a placebo or in some instances head-to-head trials and I just think it's important that we look at all the costs not just making the specific drug selection choices based on drug costs alone. All of those costs need to be considered. Thanks for considering my comments.

Dan Lessler: Thank you. And Dick Miyoshi.

Dick Miyoshi: Well, I'm the guy that has to tell you about what the work group has been doing. When we started in mental health HRSA in all its ultimate wisdom decided that maybe it needed to have other people who worked in the area think about the evidence and clinical practice. So we…HRSA got together the Mental Health Work Drug Group and it's a group of psychiatrists, nurse practitioners, pharmacists and then represented some efficacy groups, RSNs, state hospitals, community mental health centers, universities, professional organizations and the pharmaceutical companies along with our [inaudible] from corrections. And we all sat and kind of went through a lot of very hard information—the OHSU evidence, almost page by page, looked at the clinical data, looked at studies before and after, tried to evaluate that and came up with essentially that they're all…this is only on on label. We can only speak on on label because we are in the process of looking at off label. So after looking at all this evidence we concluded that they should all be on the PDL for on label [inaudible] patients. We also recommended that there

are no therapeutic interchange. There is probably a little bit of information on Clozaril that gives it a little advantage, but it has disadvantages and side effects.

All the remaining atypical antipsychotics have important differences and side effect profiles, dosing requirements and opportunities. So essentially we say that they should all be on the PDL. We're also working on safety [inaudible] essentially—age, dose, public pharmacy for both on label and off label. So our bottom line recommendations are that all the atypical antipsychotics as individual agents and have same…essentially the same clinical indications. Side effect profiles are different so essentially they all did the same thing, but side effects preclude one another whether it be metabolic things or neurologic things. We recommend that they all be on. We also recommend that there is no therapeutic interchange. Any questions there?

Dan Lessler: Thanks. Are there any questions? No. Thanks. That's all in terms of people I have listed to speak. Did we miss anybody? Why don't you come on. If you could identify yourself, please and…

James Kelly: I apologize. I did sign up outside. For the record my name is James Kelly. I'm President/CEO of the Urban League of metropolitan Seattle. I'm also the former Special Assistant to the Secretary of Department of Social and Health Services of which one of my administrations of the liaison to was Health and Rehabilitation Services. So working with all the mental health agencies. Certainly I've had the experience of working with Dr. Fischer when she worked for Medical Assistance Administration.

I want to talk to you about the support for getting access to all treatment [inaudible] validated and the atypical. From the experience that I've had in seven years with the Urban League of metropolitan Seattle…several years ago one of the most prominent cases involving the African American community was a shooting of a mentally ill patient called David Walker. Again, it was an individual confrontation with Seattle Police Department and was shot multiple times. As a result of that clearly the community working with law enforcement felt the need to have greater access to what we call crisis intervention training for officers, as well as other options that are available to protect not only our police officers, but many of the mental ill cases that the police officers deal with on a day-to-day basis. As a result of it having access to all forms of treatment was one of those things that we all supported.

More recently the Urban League is now responsible for dealing with the thousands of Katrina and the Gulf Coast relief individuals who are here in our state. Several months ago the numbers got up to close to 8,000 and now we're down to about 6,200 of which the Urban League is responsible for coordination of those services. The experience that I've had dealing with our department and dealing with all these individuals range from individuals who got off the plane, released from a federal institution, basically at least kind enough to say to us that I was just released from a federal penitentiary there for several years for robbery, but don't worry, Mr. Kelly, we only rob banks and not a not-for-profit organization. And I was appreciative to hear that.

Moreover, with the cases that was probably the most profound to us, which we are dealing with now are those who are suffering from what we call post-traumatic stress syndrome, as well as individuals who are suffering from truly schizophrenia and one of the challenges that we've had is because records, medical records were all lost down in New Orleans a lot of that information wasn't able to…readily accessible and wasn't transferable and many of these individuals because we didn't have authorization were suffering with basically hearing voices, sleeping in their cars and lucky enough through a national network we were able to meet with…catch up with some of the family members in different states to make sure that we were able to bring them here, to bring their children…their medication because a lot of folks got separated. So the bottom line is we are dealing now in this state with thousands of individuals who are suffering from a form of mental illness, particularly post-traumatic stress, as well as the schizophrenia and our position is making sure that individuals have access to all forms of treatment [inaudible] and certainly access to the atypical medication is certainly…the Urban League supports that and would ask that you do the same. Thank you so much Mr. Chairman and members of the committee.

Dan Lessler: Thank you. Yes, did you…

Theresa: My name is Theresa [inaudible]. I'm a mental health patient and I also go to Euro House for support and stuff and I just wanted to let you know that at one time I was on Desyrel and I got a doctor that said, "Oh, that's too expensive for the state to pay," and they took me off of it and I went downhill and they tried other meds and I went down…kept going further down and just before 9/11 the switched my meds all around again and I finally had to go to a private psychiatrist and he's now gotten me on meds that work and if all of a sudden I wind up without those meds, you know, I'm really in trouble because generic from Desyrel does not work. And so, you know, for once I'm doing really good and talking about going out and looking for a job, for a temporary employment job, Euro House is going to help with that and stuff. And I don't want to see that go to waste. And there is a lot of people that, you know, on meds and stuff that work and, you know, they wouldn't be able to work without it. I have friends that are doing volunteer jobs and everything and it will all go downhill if the meds change and stuff. So I just hope and pray that you guys will consider the people that are working that are on meds and the ones who want to work that are now getting better on their meds and not change them. Thank you.

Dan Lessler: Thank you. All right.

Susan: I also signed in. I thank you for the opportunity.

Dan Lessler: Can you state your name, please?

Susan: Susan Caterly(?). I'm a psychiatric nurse practitioner and I'm here both on behalf of the ARP(?) United as their president and also representing Therapeutic Health Services. Therapeutic Health Services is an agency that provides child adolescent and adult mental health and addiction care, as well as being a special population

agency serving the African American community in King County. My experience at THS has given me a unique perspective with regard to the issues related to an open, non-restrictive formulary.

The individuals I work with are generally the disenfranchised of our society. They are fearful of psychiatry and reluctant to agree to take psychiatric medication. Often they come with strongly held beliefs about individual psychiatric medication. Certainly the kind of television ads for class action lawsuits are not reassuring them that the medication offered to them is safe and effective for their mental health problems. It's not uncommon for my patients to make reference to [inaudible] when I offer a new medication that would potentially have fewer side effects. These patients already feel that they have little choice in the care they receive and when they are denied a medication they are willing to take their fears are only confirmed. Their only recourse is to refuse treatment until it is no longer their right to do so because they are involuntarily detailed.

Often I recommend a medication or class of medications for some time before the option is accepted. If there's one medication that a family member responded to or that a friend had a good experience with whether they are in the state or not then that medication they will probably take. If it's not on a formulary that becomes problematic.

Sometimes the medication I choose or the one on the formulary is rejected and I need to find a way to provide for the ones that were used. If there is a time lag between the patients' willingness to take the medication and when I can finally get authorization often times that person is already in jail or if they are a child, they are in juvenile detention.

Overcoming the fears and stigma that are cultural and psychosocial in nature is only one set of concerns. What becomes even more programmatic is to gain knowledge that the reality of genetic differences that impact metabolism and effectiveness and individual medication. Medication side effects are also commonly different in varying genetic clusters and these tend to be found in ethnic groups. [inaudible] information about weight gain has been differentiated by trust in this class. It was evidenced that African Americans were more prone to weight gain.

Every minority group such as African Americans have not been included in the clinical trials in a substantial way, which makes it problematic to look at evidence-based practice. The other groups that I work with are people with co-occurring disorders who have had toxic [inaudible] to their brain and their medication responses are not going to be similar to the ones in clinical trails either.

And then the final group that this organization works with is children. When children are ready to take a medication and their parents are willing for them to take it, there's a critical time length and if we miss that time length then we have a child who's not treated. And often times that's a child who ends up not in school or in juvenile detention and I urge you to consider this open formulary specifically for these special populations. Thank you.

Dan Lessler: Thank you. Have I missed anybody? Have we missed anybody here? Okay. Thanks. I think Dr. [inaudible] I'm just going to open it up for discussion here with the P&T Committee, but I didn't know if you wanted to…if you had any comments at this point or anything you'd like to say before we…

Woman: Well, I think what the public testimony has really emphasized to me and I just wanted to repeat it is the extent to which the medications need to be individualized in order to be effective, but also to be acceptable.

Dan Lessler: Thanks. Jeff, did you have a comment? Okay. So at this point I guess what I'd like to do is just open it up for committee members just to elicit people's comments, observations at this point. Sort of to begin a discussion that moves us towards some kind of decision here. So…

Vyn Reese: Hi. I'm Dr. Reese and I wasn't here at the last meeting. I wasn't here at the last meeting, but I did read the transcripts…I read them several times and I listened to the testimony today and read the material and I think this class of drugs is a lot like cancer therapeutic drugs where you really can't therapeutically interchange them. They have distinct indications in small subgroups and you can't manage them as a group very well. I think you need to have them all be on the PDL. It seems like that is a logical thing to do. At this point in time there is no evidence to say that's not the best way and I think that's the best way to serve the population at risk. So…that would be my thought on the matter.

Dan Lessler: Angelo?

Angelo Ballasiotes: Angelo Ballasiotes. Can everybody hear me? Okay. As being a clinician in treating people with mental illness, especially [inaudible] populations with [inaudible] and creative disorders I don't find any way that…out of the situation in that we do have to individualize treatment for these people. So I do advocate for an open formulary and also limit [inaudible] substitution.

Dan Lessler: Alvin?

Alvin Goo: Hi. Alvin. I think we all agree that this is a difficult class, but at the same time for such a large problem it's sort of shocking and disappointing that we don't have great evidence to help define which medication would be better and that it's difficult to determine which agent is going to work best for a patient considering their individual characteristics. There are certainly differences in pharmo dynamics and pharmo kinetics, which may or may not relate to better improvement or outpatient outcomes. So that recognizing and the fact that it is going to be difficult I think that also it would be…I'd like to sort of recommend that the work group…they've done a great job and I know they've put a lot of hours, but I'd like to assign them with developing some sort of step wise approach to help with the primary care physicians when they are covering patients that need antipsychotics just to gain them some assistance because they are so…there's not enough evidence to help direct them one way or the other and I wonder if it would be reasonable to

ask the work group to come up with some sort of step wise approach without limiting the agents.

Dan Lessler: I think we're going to have more discussion when we reconvene as the DUR and so what I was going to ask is if we could table that request and discussion of your request until then. Okay? Other comments or observations at this point? It seems like…at this point there seems to be a developing consensus that all of these drugs need to be accessible because of their…each having a unique characteristic both in terms of when they are going to be effective, as well as side effects. Okay. Well, it seems like there not being any more comments I'm wondering if somebody would like to make a motion here? Angelo, you want to?

Angelo Ballasiotes: I'll make the motion here and see how it goes. After considering the evidence of safety, efficacy…

Dan Lessler: Wait a second. There you go.

Angelo Ballasiotes: After considering the evidence of safety, efficacy and special populations for the treatment of mental illness, schizophrenia and bipolar disorders, I move that the medications of aripiprazole, clozapine, ziprasidone, risperidone, quetiapine and olanzapine is safe and efficacious…no single medication is associated with fewer adverse events in special populations and these medications cannot be subject to therapeutic interchange in the Washington preferred drug list.

Dan Lessler: Is there a second? Okay. The motion has been seconded. Is there any further discussion or comment at this point?

Carol Cordy: The one sentence…Carol Cordy. No single atypical antipsychotic is associated with fewer adverse events in special populations. Is that actually true based on the evidence that we've…? I mean it seems like some of them are…do have more adverse events. I'm just not sure we need to include that sentence.

Dan Lessler: If we take that as a friendly amendment perhaps because I think if we take that out that would be okay and then we're not left with all the nuance that exists here. So why don't we delete that, Donna. We'll take that as a friendly amendment. So is there any other discussion?

Dan Lessler: You're…Duane, you're shaking your head, but in the past we sort of have…

Duane Thurman: This is Duane Thurman. That's the implied assumption that this is the decision…this gives us instructions as to how we deal with them on a…it assumes we are putting them on the preferred drug list pursuant to their recommendation.

Dan Lessler: Yeah, are safe and…yes, I think…thanks, Donna. I prefer in this case just being very…as clear as can be and I think that is as clear as can be. So I appreciate the comment. All right. So I'll just read this one more time. The motion that is on the table is…we did have a second, right? From Ken.

So after considering the evidence of safety, efficacy and special populations for the treatment of bipolar disorder and schizophrenia…this is Angelo who has moved that aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, and olanzapine are safe and efficacious and should be included in the Washington preferred drug list. Atypical antipsychotics cannot be subject to therapeutic interchange in the Washington preferred drug list. So that motions been seconded. There being no further discussion I think we can vote. All those in favor, please say I.

Group: I.

Dan Lessler: Opposed same sign. Okay. The motion passes and I think that's it. I appreciate everybody's input and the discussion. I think at this point, actually, we can…we will probably adjourn for a few minutes. Jeff, do you think? And then we will reconvene with the Drug Utilization Review Committee.

Woman: The following portion of the tape is the Drug Utilization Review Committee from June 21, 2006.

Woman: Next to TVW the Washington State Board of Pharmacy and Therapeutic Board convenes a public meeting in SeaTac on June 21st.

Dan Lessler: So if we could reconvene here. The first item of business actually is that we actually have two sets of minutes from December and February that needed to be approved. They are in the back of our binders and I wanted to ask if there was a…maybe we should take these…or one at a time…so maybe we could begin with December minutes and wanted to ask if there is a motion for approval?

Man: I move they are approved.

Dan Lessler: Is there a second? Okay. All those in favor?

Group: I.

Dan Lessler: Okay. And then the February minutes. We could take a quick look at those, as well. And, again, is there a motion for approval? And a second? All right. All those in favor?

Group: I.

Dan Lessler: Okay. So the December and February minutes are approved. And actually what I'd like to do if I could, Siri, is I was going to turn it over to you and maybe you could just describe the structure of the afternoon and the DUR. I know you have some people you'd like to introduce, as well.

Siri Childs: Okay. What's on the agenda for the DUR board meeting this afternoon is a couple of things. We are going to start with the mental health stakeholders work group recommendations regarding age and dose limits on the on labeled use of the atypicals. But before we start that…and then also we are going to have a presentation from Dr. Paul Shekelle on the off labeled use of the antipsychotics.

That's going to start at 3:15. So we hope we're going to wrap up the first part of this program by that time.

Before we get started though I wanted to introduce a very key member of our HRSA staff who works hand-in-hand with Dr. Thompson. I'd like to introduce Jonell Blatt. All of you who are working with us on the mental health stakeholder group have heard Jonell's voice on the telephone, but maybe you haven't seen her before. So I'd like to introduce Jonell Blatt to you. I kiddingly say she's the person that makes Dr. Thompson look so good because she really takes his ideas and she makes them happen. So thank you, Jonell, for being here.

I would like to get right into a presentation and I'd like to introduce a member of our work group, Dr. June Bredin and she's going to present the PowerPoint and the recommendations to the board.

June Bredin: I want to start out by saying that our recommendations really go in line with the testimony that we already heard that all of these drugs have a place and so what we focused on rather than a preferred agent was safe use and we're still ongoing in discussions as far as multiple drugs and off-label indications, but our very first line being safety we wanted to talk about dosage—appropriate dosage ranges, as well as…and then I think our next look is probably going to be at multiple drugs within the same class. If we could look at the next slide, please.

This looks like a busy slide, but really isn't. I think one of the areas that we've been most concerned about is the appropriate use of these medications in children, especially children under adolescent ages. In my particular practice with children with disabilities and autism these medicines are used in school-age children, but they need to be used very carefully especially as you see in the under 3 and 3 to 5 year age groups here. Under 3 there is a 0. That doesn't mean they can't be prescribed, but if you look at that star underneath it says, "Under 13 requires a designated expert opinion." And what we're trying to do rather than limit access is actually open up access so that provides that are really seeing these children in the community have access and backup to somebody that could help them with appropriate prescribing. It is very difficult in a young age group and if you notice the second star at the bottom it says, "That the EPA criteria will be developed for emergent use." So that is acute behavior crisis that somebody is not going without in an emergency.

The first two rows here…what we started out with, information of what was really happening in our communities…first was the FDA max for the dose work would be in adult for all the drugs in the drug class, as well as one or two state hospitals are using as their consensus maximum. And we did some [inaudible] finding. There are some drugs that we juggled it a little bit based on what real community practice is and if you go all the way to the right of this slide that's what our work group maximum…that's what we came up with as a work group as what was a community standard for acceptable dosages without [inaudible] typically say…without stopping and taking a big breath. Having some kind of look at very high doses where side effects may be more prominent. So now if we go on to the next slide in working with…trying to come to this consensus we looked at the

different age groups and in those age groups looking at the number of clients who were using atypicals specifically the children, the number that were above the recommended doses that we had discussed and then adult average daily doses and for…kind of an explanation of the age group classes that we made in children we made the under 13 and over 13 cut based on state law that at 13 children are considered emancipated and they look for mental health care independent of their parents. Additionally, as you move into the adolescent age group you have the emergence, especially in bipolar and other psychotic illnesses. So it becomes a population that starts looking psychiatrically more like an adult than a pediatric population.

Then looking in the under 3 and 3 to 5 year age group that was where we were most concerned about usage and these are children that are not in school and still have developing brains. These drugs for children have mostly been studied in developmentally delayed and autistic spectrum disorder indications and most of those studies are in school age children. So we took more caution with under 6 group and then also tried to make some dosage levels that would be appropriate for average weight within the age group, as well. So moving on to the next slide.

This is just reminding us the trade versus generic names of the drugs we're talking about. Next slide, please.

This is our current data in the under 3 year age group. We only have one client currently on Medicaid that is on risperidone, but moving into the 3 to 5 year age group for the next slide this is very different. In this state already we have 129 children on atypical antipsychotics between age 3 to 5 and based on the dosage recommendations we made 40 of those children, a good 25% are above the recommended dosages. Next slide, please.

When you move into the age 6 to 12 group you see a huge increase to over 2,500 children. And, again, over 10% of them are above the dosages that we recommended. Now some of that is because some of the drugs don't have good indications yet and our recommended dosage without an opinion is 0, but this is the data as to why we needed to look at pediatric age groups and why we needed to make some recommendations based on safety.

And then the next slide actually shows a fairly similar number in that adolescent age group.

And then the next slide shows that we have 22,000 clients in the adult non-geriatric population and average doses for those different drugs. Those are [inaudible] is incredible and I think looking at the long-term data it's going to be the next challenge for the Mental Health Work Group especially if then we not only have to look at dosages, but people that may be on large doses of two or three of these drugs at the same time and that may again be appropriate for some people, but it should be looked at a little more closely.

Then the last slide about ages…the age 60 and over group, again, is a different sub population that we're going to have to look at. Many of these clients may be

people who are aging, into the geriatric population, but actually have underlying psychotic illness. The other issue then though becomes the appropriate use of these drugs in somebody who does not have pre-existing psychiatric illness, but who becomes demented, especially with the recent FDA black box warning.

So this kind of gives you the overview of how we set up that chart thinking of…the only thing rather than trying to limit access by drug was looking at safety in doses. And I think that's it, isn't it? One more. So we are requesting that the DUR board adopt our drug… Work Group's atypical antipsychotic safety recommendations by age and dose and to help providers in working through this we are agreeing that in patients who come up for an edit that the prescription history and the [inaudible] patterns by payment. In other words the records of what prescriptions the patient is actually picking up will be provided to the provider and then they see whether people are actually picking their drugs or seeing multiple providers and if we work on communication and education in this regard, continuing to work with stakeholders within and without the Mental Health Drug Work Group and as I eluded to earlier trying to develop especially in pediatrics a network to expert opinions, because not everybody can get to the experts, but their knowledge needs to get to the clients. I'd like to thank you.

Dan Lessler: Thanks. So I guess at this point we could open it up to the committee for questions and comments. Is most of the [inaudible] here done by psychiatrists or by primary care physicians? Who is writing the prescriptions?

June Bredin: It's a wide variety. It's primary care, it's neurology, child psychiatrists, pediatricians, family doctors.

Dan Lessler: And do you have any sense of the indications for which the medicines are being mixed?

June Bredin: The problem is obviously in the claims based data. Medicaid doesn't get that information. Maybe Siri could talk about that a little bit more.

Dan Lessler: Siri, you want to?

Siri Childs: Dr. Bredin is exactly right. On our current system of claims processing we don't look at diagnosis at all. If the physician orders it…unless it hits some kind of safety [inaudible] that is programmed into the computer separate from an indication we don't know what it's being used for.

June Bredin: And I think that's exactly our logic is asking for the edits in the very young age groups is to make sure that the really high risk population is being reviewed by somebody with expertise in the field.

Jeff Graham: Excuse me, Dan, as a person who gets to have the opportunity to sit on this work group I wanted to point out these are maximum doses. I mean when we say these are the recommendations. These are not really the doses we'd recommend the children, but that would mean the maximum dose they would receive. Sometimes

people look at those and say, "Oh my heaven, that is a very large dose." This is a maximum dose. It's not what the normal dose we would consider.

June Bredin: Especially when you look at risperidone on the top line of the recommendation chart. When you look at the FDA maximum when it first came out it was 16 mg and we had a lot of interesting discussion in the work group because people don't use risperidone at that high of a dose. And we came up with the 9 mg dose by no clinical practice for adults. The lower dose, like a 2 mg, are used for children. In autistic spectrum disorders that's what the research says that low dosing the psychotic means…there's some pretty vigorous evidence that it has efficacy in that population, but only at low doses.

Dan Lessler: Siri, did you have a comment?

Siri Childs: Well, I felt compelled to say what Jeff Thompson would say in response to Dr. Graham. What Dr. Thompson would say is that these are the maximum doses. This is the point at which we'd like you to take a deep breath and, you know, take another look at it.

Dan Lessler: Wondering if there are comments or questions from…Carol?

Carol Cordy: Can you review with us the process you want us to accept your recommendations and then where will that go if a patient is on higher than maximum dose. What will be the process to contact the prescriber and…

Siri Childs: At this point in time we are asking you to accept these recommendations and these age and dosage limits would be implemented with the preferred drug list implementation in October. We'll work with the work group to further define any other safety edits that we would apply, you know, at that time. Everything that we would like you to approve this at this meeting and as we work with the work group we'll be bringing back to you other bits and pieces regarding poly pharmacy and other off label use. At the August meeting and possibly at the October meeting. But at this meeting we would like you to at least give us the authorization to proceed under the age and dose limits.

Jeff Graham: This is Jeff, again, what happens when you take a deep breath?

Siri Childs: The deep breath is another word for prior authorization.

Jeff Graham: And what…I guess we say here what things are going to be developed for that prior authorization is that correct?

Siri Childs: Right. And right now the work group is recommending, and we'll do further work on this, that if the child is younger than 13 we will ask for a second opinion similarly to what we've implemented with the ADHD drugs, but so far that's the only direction and the work that we've done with the work group. The other very strong underlying principle that Dr. Thompson has is that whatever we do will enhance access. It will not block access.

Bob Bray: I guess that was my question. This is Bob Bray. The HRSA designated expert opinion is…would be whom? I mean somebody from the community that you all decided is that expert or is it someone that is an in-house expert? And how is that going to happen? A phone call, a specific form that's filled out or…? What was the thought there?

Siri Childs: Well, we are trying to pattern after our learnings from our ADHD program and our ADHD program has incorporated child psychiatrists and child behavioral experts at Mary Bridge and Children's Hospital and right now the second opinion involves first a paper review, a chart review, but it can involve a telephone consultation or it could actually involve physically seeing the patient, but it is another step in the process to provide consultation to the prescriber.

Man: Siri, how comfortably can that work if it was in our clinic that we had a problem with one of the psychiatrists wrote…has been writing for a drug over-and-above and he was pretty confused with how to get that expert opinion. There was no information sent to him or anything like that.

Siri Childs: If it is a child and if it hits our edit the prescriber will receive a fax for additional information, plus information for the prescriber to get a second opinion from a second opinion that is located in that geographical region. I did forget to mention Sacred Heart Hospital in Spokane, too. Sorry. But there will be information that is sent to the prescriber identifying a second opinion option in their geographical area and directions on how to obtain a second opinion prior to even ordering the drug if they know that it is going to hit a safety on it. Other than that if it just hits the edit then we'll contact the prescriber and help arrange for that second opinion, too.

June Bredin: And begin remembering that we're talking about new starts because we feel protection applies. We've talked about beginning some process to look, you know, if they are over the safety edits and they've been on that drug to be reviewed, but it would be…there would be a continuation of care while that process was going on. And additionally remembering that second line there at the bottom that we're going to develop a process for emergencies so that the prescription could be initially filled in an emergency situation until that review occurred.

Alvin Goo: Hi, it's Alvin. I just had a question about the max dose on the olanzapine, quetiapine and risperidone. So those are…before we look at it is it going to exceed the FDA approved dose before you take your deep breath? And I just wanted to know…I'm not too familiar with the P450(?) enzymes on these or how significant it is, but they are 3, 4 and 286(?). So I didn't know if we wanted to just stick with the FDA recommendation max dose before we review it or you've looked at and feel that the drug interactions are not significant.

June Bredin: It was kind…it was a, I guess, a toggle to get the process because in this class of drugs…in drugs like risperidone we actually went under. We were looking at what current community standard of care is, as well and looking at the data of what is commonly prescribed and I think that with Sharon Farmer and her folks who, you know, the psychiatrists who are most comfortable with what were the appropriate doses I think that's where we really ended up with those.

Angelo Ballasiotes: This is Angelo Ballasiotes, again. I find these doses very reasonable the way they are right now, the maximum doses. And then if there needs to be any fine-tuning or anything like that we can do that later on. I feel pretty good about it.

Jason Iltz: This is Jason Iltz. Just a point in clarification. When you talk about dosage and age recommendations was on label use implied within that or is that a whole separate issue that you're looking at?

June Bredin: It's actually a whole separate issue remembering that the [inaudible] are getting made on claims data. So the diagnosis isn't available in this process right now. So we were…bar and having that information available this is more on a safety basis rather than an on versus off label basis.

Jason Iltz: And so you're anticipating down the road having some sort of process at least suggesting a process maybe for certain age groups where there is some sort of hard edit that asks for an appropriate indication and because in my mind that's a safety issue as well. I'm really concerned that there is that many people under the age of 5 on these medications and we don't know why. I want to give prescribers the benefit of the doubt that it's appropriate, but I would like the data to be there for us to be able to make that conclusion.

June Bredin: I agree absolutely. And actually in the discussion…the initial proposal was to allow risperidone and olanzapine in the young people without that safety edit and I as a primary care provider who actually does this prescribing said, "No," mostly on the basis of wanting to increase the availability of that backup and second opinion.

Gary Franklin: Yeah, this is Gary Franklin from L&I. These are general safety criteria for age and dose immediately applicable to on label use and until we make decisions on off label use they will still be applicable there but we may make other decisions as well as that more detailed discussion on off label use as we'll start the day with Dr. Shekelle here at 3:15 as that moves forward. Is that theory setting?

Siri Childs: And I've got…this is Siri from HRSA. Clarifying that when we implement this drug class in October we'll be working with our current point of sale system and I'm happy to say that within 2007 as we roll out some of these other initiatives we will be in a different claims processing system that allows us some more sophistication and, you know, you name it we'll be able to do it. But right now as of our October implementation we're pretty well stuck with what we've had since 1979.

Dan Lessler: So Siri will that then allow you to connect a diagnosis with…

Siri Childs: We'll be able to do steps therapy, you know, as Donna described earlier. You can look back in history and see what drugs they've been on prior to approving, you know, a specific drug. If they've been on the preferred drugs. I mean just think how that's going to help our preferred drug list if they tried and failed the preferred drug then there won't be any stops, you know. So we're really looking forward for

all of our prescribers and for us to have a more sophisticated, more smart PA system.

Dan Lessler: And our…is it just a few providers that make up most of the prescriptions for the medicines in children? I mean particularly the younger age groups or are there a large number of providers writing a small number of prescriptions?

Siri Childs: I'll have to get back to you on that one.

June Bredin: I guess my impression as a secondary provider who is getting kids into our facility is there are a fair number of different providers and different specialties.

Dan Lessler: So it's a number of providers with different specialties? So I guess my other question would be what efforts are going to be undertaken just in terms of generally educating this group of providers around appropriate prescribing? Obviously you're starting here. You start looking under the light here because you've got the dosing information and you're gonna…I think we're going to be talking more about off label use and then there are issues about polypharmacy and so forth. So it seems like there will be a laying as you roll this out and I'm wondering how you're going to educate providers about, you know, about all of this?

Siri Childs: What we plan to do is to use our contracted service with ACS in their IBM and TAS program that you have seen reports from last year. They will target those specific prescribers and for the top 120 prescribers they will actually get a face-to-face visit, discuss the specific clients that those prescribers have. So it will be a pretty complete intervention and educational program.

Bob Bray: This is Bob Bray. I have to make a political statement. As a primary care physician and…especially on the east side of the mountains, the problem that I can foresee, the unintended consequence of all of this good work is the sense of, "Well, primary care physicians have somebody available maybe on a phone or maybe responding to a fax," and so there's been a consultation. So primary care physicians should do this. You can do this. And the frustration that I have is when there isn't proper access to specialty services I become really smart and so I guess I would also…even though we're talking about the PDL and drugs and the DUR I would really hope that we also…the powers that be can address the issues of access to psychiatric services for both children and adults because it's really difficult and when we have really difficult patients I can prescribe the drugs, but that's not the services and I…so anyway, I had to make that political statement.

June Bredin: I think as a [inaudible] Mental Health Drug Work Group I do the exact same thing. I think Siri and Jonell will vouch for me here.

Siri Childs: And one of the last things that Dr. Thompson told me in preparation for this meeting is be sure to stress that this last asterisk that says EPA criteria will be developed to facilitate access for emergent use, he wasn't talking about just the drug. He was talking about the consultation services that he wants to increase, expand and network so that you have help.

Carol Cordy: I just wanted to tag on to what Bob had to say that it's not just the east side of the mountains.

Jeff Graham: This is Jeff Graham. I think Jeff Thompson has made a commitment. If he can't do the five things he says at the top, if he doesn't think he can implement these dosages, which is unfortunate. They do need to be done, but they have to be able to be met before he can do this. And now that HRSA also has mental health and developmental disabilities within that same grouping in DSHS he can work with those people much closer who…on the state level can help implement some of these things at the mental health level and so forth. I'm not saying that he's 100% confident he's going to be able to deliver, but he's very positive about being able to move this forward.

Siri Childs: I'll just add another comment that he really has committed to this process and to the point where we won't move forward until he feels that we can provide a good product.

Dan Lessler: Are there any other comments or questions? I just want to clarify one point in terms of when there will be an intervention. Clearly it's when a new prescription gets written for a dose that sort of triggers, you know, triggers a review, but I am curious just to…I think I heard you saying that if somebody is already on a dose that exceeds the triggering dose they would still get the medicine, but will there then also be a review?

Dan Lessler: Okay. Okay. Are there any other questions or comments from committee members? So…and Siri, I don't know if you or any folks have any additional comments about this? I guess what would…sounds like what you need from us is just a formal endorsement of this program. Does it have a specific…just the AAP's safety recommendation? Is that what we would…?

Siri Childs: I think you should specify age and dose on it.

Dan Lessler: Okay. Is there…would somebody be willing to make a motion to endorse these safety recommendations including the specific doses as…or can we just say as outlined in the memo of June 20th to the committee or something like that?

Siri Childs: Can I stop you just a minute?

Dan Lessler: Yes.

Siri Childs: We normally have stakeholder input for the DUR activity, too.

Dan Lessler: Oh, okay. I apologize. So why don't I stop there. That's my error and ask. Do I have sign up sheets? No. Please, so why don't people come forward and if we could identify who you are representing, if you're sponsored and I'd ask that you limit your comments to three minutes, please. I'm concerned that that microphone might not be on there.

Adam: I'm Adam NAMI Washington. I'm not sponsored by anyone and I sit on the Mental Health Drug Test Group. We came into this process with open access and safety being the primary concerns of NAMI Washington. In our work groups and I facilitate our support groups in south King County. We hear time and time again about things that we suspect aren't quite right. So when the data came out on children under the age of 6 particularly I was both horrified, but not surprised. I've been hearing these stories from parents and other people who are concerned that they…quite frankly their kids and their loved ones are being over-medicated basically and there doesn't seem to be a way that they can have any assurances that what they are getting is right because when they change doctors the dosage and medications normally always change, too. And a lot of these people change doctors frequently for a variety of financial reasons. Consequently, when we came to this…this has been one of the things that I get very concerned about and I understand all the concerns about messing with somebody else's sandbox and who are we to be telling you these things, but the thing that distinguishes us is we have a range of experience that's not matched in many places in the state, and secondly is that we really did hard work on this thing and we called in all the expertise we could find and we reached the point where we're concerned that…our concerns that somebody may accidentally do something or kind of lesson because now we have a professional approach, which satisfies…I'm an engineer. The scientific background that we bring to the table and in concern for the loved ones we deal with. So my organization supports this whole-heartedly and we just want to carry it not to an enological extreme, but to the point where we all have confidence that the people prescribing to our loved ones across the state are following some kind of guideline so at least they are starting off with a healthy dosage, which will lead to some positive outcome whereas many cases I hear we're starting kids and other people at maximum dosages the first line and so that's why NAMI supports this proposal.

Dan Lessler: Thank you. Are there other stakeholder input? Okay. So thank you for reminding me, Siri. So with that, again, I wanted to come back to the committee. Is there…previously there was no further comment. I'm assuming there's no further comments at this point. And we'd like to ask for a motion with respect to the AAP safety recommendations.

Bob Bray: This is Bob Bray. I move that we accept the Mental Health Drug Work Group recommendations for age and safety recommendations as outlined in the June 20th memo from Mental Health Drug Work Group including the recommended maximum dosing for adults, as well as the age related maximum doses for children.

Dan Lessler: Is there a second? Okay. Any further discussion? All those in favor say I, please.

Group: I.

Dan Lessler: Opposed, same sign. All right, I think the motion passes. Very nice piece of work. I appreciate the efforts of the Mental Health Work Group. At this point, Siri, I think we're going to be…do we have something else before Dr. Shekelle?

Siri Childs: We have one more thing. I would like to personally thank all the members for the hard work that they did on the annual DUR report. I've got to tell you that it's in the internal review at HRSA right now. That it will be printed up, bound I think for the first time so that it's in a nice book form, sent to CMS on the 30th of June. So you'll all get your copies here. Thank you, again.

Dan Lessler: Thanks. And I believe Dr. Shekelle is going to join us at 3:15?

Siri Childs: Uh huh.

Dan Lessler: So maybe we should take a break or touch the time with people calling in. If people could come back around 10 after 3 so that we can…right, so we can start on time when Dr. Shekelle calls that would be great.

If we could reconvene. If people could take their seats, please. And the next discussion we're going to be entertaining here has to do with off label use of atypical antipsychotics and actually Dr. Gary Franklin is here, Medical Director of Labor and Industries who has been involved in the development of this work and so Gary and Matt if you could just provide some background and then when Dr. Shekelle comes on if you could introduce him as well, please.

Gary Franklin: The agency Medical Directors Group, which is an informal group of all the health care agencies that meets with the Agency Medical Directors and other health policies here. We've been doing many things over the last several years, but one of the things we've done is obtained some funding from the agency for Health Care Research and Quality a couple of years ago to do an evidence-based medicine conference. We actually have new money to do something later this year, December 4th and 5th, on [inaudible] performance and then two falls ago in 2004 we did an application for the agency for Health Care Research and Quality to actually fund an evidenced-based review for off label antipsychotics. So instead of the states prescription drug program finding an APC to do the systematic review, which as you know is the most resource intensive part of this whole thing. We actually competitively applied to have the AHRQ funds systematic review and they accepted the review and they assigned the review to the RAND Corporation. Dr. Paul Shekelle who is going to be…we're going to be on the phone with him at 3:15. Hi, Paul, it's Gary Franklin. How are you doing?

Paul Shekelle: Hi there.

Gary Franklin: I'm going to introduce you here, okay.

Paul Shekelle: Okay.

Gary Franklin: Paul is an MD, PhD and is a consultant in health sciences at RAND and since 1997 has been the director for the Southern California Evidence-Based Practice Center at RAND, which is one of the 13 or so evidence-based practice centers around the country. The Oregon EPC that has done quite a bit of work for this committee is another EPC [inaudible] AHRQ. Dr. Shekelle is also a Professor of Medicine at UCLA…at UCLA School of Medicine and is a staff physician at the West LA VA

Medical Center. So without further ado Paul has gotten together a presentation and has directed this entire review of off label antipsychotic use. So Paul I will just hand it over to you.

Paul Shekelle: Yeah, sure. What would help me, Gary, is if you first gave me some sense of how many people are in the room and what their backgrounds. Obviously I don't need to be introduced to every single person, but is this 5 people? Is it 50 people?

Gary Franklin: It's thousands of people, Paul.

Paul Shekelle: [laughing]

Gary Franklin: I think I'll let Dr. Lessler, the chair of the Pharmacy and Therapeutics Committee tell you a little bit more about the environment.

Dan Lessler: Dr. Shekelle, hi, this is Dan Lessler. I'm the chair of the committee. We appreciate your being with us today to provide this presentation. By way of background we have the Drug Utilization Review Committee here, which actually has a diverse representation of clinicians on it—physicians with different backgrounds, general internists, family practitioners, nurse practitioners, pharmacists, physician assistants. So actually a lot of these…

Paul Shekelle: Okay. So this looks like a P&T Committee. Is that right?

Dan Lessler: That does, but as well we have stakeholders in the audience, probably I would say about 25 or 30 people representing different groups and then as well members from the state agencies here, as well.

Paul Shekelle: Okay. Great. And then the other thing is I'm not sure that Jaymie passed this on to Gary, but she told me that you would pay me for this time, but I told her that instead I would forego that as long as Gary re-directed that money to buy the staff dinner.

Dan Lessler: Thanks. So we've got you keyed up here with, you know, with your title slide and you can take it from there and somebody can…we'll move through the slides as you let them know that it is time to change.

Paul Shekelle: And I'm sorry I can't be there in person. I would normally like to have done that, but I'm a member of an institutional review board, which meets the third Wednesday of every month and so I went there for the first two hours of the afternoon and now I've come over here, but that's why I couldn't be there in person. At any rate, I don't have a lot of slides prepared just sort of the high points because I wanted to give enough time for the give and take that's necessary for people to get any sort of contextual interests or questions out on the table. But as you heard in the introduction this project got its start in life with a nomination from Washington State, the AHRQ to be an efficacy and comparative…well, initially to be a study of off label use of anti-psychotics. Okay? And it's gone through a couple of changes that I'll discuss as we go through this. So if you go to the next slide these were the original…and for the people who are not familiar with the

evidence-based practice center program there is some evidence-based practice center jargon of which this is one of them. These are the key questions—these are the questions that the people that send in topics to AHRQ for funding, these are the questions that they list as the ones that are important to them and then AHRQ then in turn farms these out to us.

So first let's just review what these original key questions are and then what are the leading off label uses of antipsychotic drugs in the literature? That was number one. Number two, what does the evidence show regarding the effectiveness of antipsychotics for off label indications, such as depression? And how do antipsychotic medications compare to other drugs for treating off label indications? And number three, what subset of the population would potentially benefit from off label use? And then obviously the next slide.

Number four, what are the potential adverse effects or complications involved with off label antipsychotic prescribing? And then five, what is the appropriate dose and time limit for off label indications? There was a sixth key question about cost effectiveness that was dropped very early on because there wasn't going to be sufficient data or resources to do that question.

So then we will move to slide number four. Initially we had a discussion with representatives from Washington State along with members of a technical expert panel that we put together about sort of within this relatively large set of questions. One of the areas, one of the more precise areas of interest and the first one that came out is that this was not really about giving generic haloperidol or something to people. This is about the high cost atypical antipsychotic, not counting clozapine because of its highly restricted use due to the blood test monitoring that's necessary. So the first change was that this went from off label uses of antipsychotics to off label use of atypical antipsychotics. And then the second change was instead of doing key question one and sort of…which is sort of an entirely different literature, you know, sort of looking at utilization data we asked Washington state, you know, they must know their own utilization data. What are the main areas of interest for off label indications? And that's the list that you see on this slide—behavior disorder in dementia, depression, OCD, PTSD, personality disorder and then as a bonus if we can do it and we did, which is why it's on the slide, Tourette's and autism. So this became…so the intermediate version of this report was what is the evidence for these efficacy of atypical antipsychotics in these particular conditions. Now before we move to the next slide it then further underwent one more change where it was folded into a new program that HRQ is doing called the comparative efficacy reviews, which focused mostly on comparative data within drug class. Similar, but not exactly the same as the DUR project and people around the table are pretty familiar with the DUR, is that correct? Yes? No?

Dan Lessler: Yes.

Paul Shekelle: Yes. Okay. Yes. Okay. So that whereas the original key questions that we got had to do with what is the effect of, you know, drug A compared to placebo about efficacy or was the effect of drug A compared to a standard comparator drug like a

typical antipsychotic or a typical antidepressant. With the move to the CERs there was also the added emphasis on differences within class. So what's the difference between drug A and drug B or drug A and drug C within class? And so that's…all of those changes are then reflected in the report.

All right. So now we're going to skip over entirely the methods. There is a report and you can quiz me on them if you like, but I don't think that's the subject of your interest other than to say that we conducted the standard EPC program level of rigor in terms of methods. We ended up screening…you should now be on slide five. It has a little flow chart. Is that correct?

Dan Lessler: Yeah, that's where we are.

Paul Shekelle: Okay. So we ended up screening 2,700 titles to look at 144 articles assessed as relevant of which 129 were controlled trials, mostly randomized controlled trials, obviously. And 15 were observational studies of a certain size, which are looked at just to help flush out the data on adverse events because of the problem with rare adverse events.

And so then the next slide now…each of these slides will just discuss in brief sort of the high points for each condition. So in terms of behavioral disturbances in dementia and probably most people are the table…or pardon me, the second pull apart most people know, but…wait a second, I'm getting a head of myself. Those are the risks. In terms of the efficacy the same group that published the JAMA(?) meta-analysis last summer about the risk of death. Okay? Published…while our review was in draft form meta-analysis of efficacy that included 15 trials and because they had a few trials was the Dains(?) data that we didn't have. We went ahead and substituted between our draft report and our final report their analysis for…what our analysis was. But any rate their analysis was 15 trials and there was this evidence of a small, but statistically significant benefit for risperidone and aripiprazole. Okay? The other two drugs didn't reach a…the evidence from it was sparse or conflicting for olanzapine or quetiapine and there weren't any ziprasidone studies that were identified.

Next slide. For depression this all reflects our own analysis because there is no existing review or meta-analysis on that. For patients that have SRI or SSRI as the case may be resistant major depressive disorder, direct comparisons of augmentation therapy with atypical antipsychotic and an antidepressant versus just the antidepressant alone did not show any evidence of statistical benefit at eight weeks although in three studies the onset of benefit was faster in the augmentation group. The second bullet point, the evidence is very sparse and conflicting about whether these are good as monotherapy for major depressive disorder with psychotic features when compared to conventional therapies. And similarly is sparse and conflicting regarding atypical antipsychotics and bipolar depression. Okay? Compared to conventional therapy. Obviously it's an approved invitation for mania. And aripiprazole has not been the subject of any studies for this particular indication.

All right. Then the next slide for OCD only risperidone, olanzapine and quetiapine have been studied. We performed our own meta-analysis of this from nine randomized trials and what our finding was is that there is a critically important beneficial effect when these drugs are added as augmentation therapy for people who are selected into the study because they failed to respond to SRI therapy. Now you should know that since our report was finalized there has been a completely independent and unfortunately precedent to our attempt to independently publish this, another group that also did a meta-analysis of OCD for atypical antipsychotics and included the same nine studies, got a little bit more patient level data so that they were able to correct the percent of improvement for what's called a responder. In our study we relied on what the…what the a…all these studies dichotomized the results into responders and not responders and picked some level of change on the Yale Brown(?) obsessive compulsive disorder scale as the threshold for what the responder and some say 25% and some say 35%. This other group was able to standardize all of that and I can't remember whether they standardized on 25 or 35, but they standardized on something. They basically came to the same conclusion is that there is this statistically significant benefit for adding a atypical antipsychotic to an SRI and SSRI-resistant patients. There is much more data and they achieved statistical significant by themselves for stuff for…well, not much more, but there is like three studies…four studies, three studies and two studies, something like that. And the data for risperidone and quetiapine independently achieved statistical significance when you just pool the studies of those drugs alone. Okay? Whereas olanzapine does not. All right? And…but there is no evidence…and there is statistical evidence of heterogeneity, but there is not evidence to say that one of these is necessarily different than the others in terms of efficacy. [inaudible] been using an indirect comparison. Obviously they've never been compared head-to-head.

All right. Next one. And these last set of slides go pretty fast. PTSD only with risperidone and olanzapine have been studied. Evidence is inconclusive.

Personality disorders – next slide. Only olanzapine and risperidone have been studied. The evidence is inconclusive.

Tourette's – next slide. Only risperidone and ziprasidone have been studied. Okay? Evidence is inconclusive.

And lastly – autism. Only risperidone has been studied and only in two trials. Both of them report improvement in patients with serious behavioral problems in children with autism although the caveat is that treatment has only been extended out as far as six months in duration. And as opposed to some of these conditions this might be an area where treatment would have to be buried for a long [inaudible].

All right, next slide – adverse events. The evidence is consistent that olanzapine is associated with more weight gain than placebo or the other atypicals or the typical antipsychotics. Now the second bullet point is the [inaudible] meta-analysis that most of you are probably familiar with and then the independent, but highly related FDA analysis from last spring that led to the black box warning on atypical

antipsychotics increasing the risk of death in elderly patients with dementia and agitation. Now what you may not know is that the third bullet point…this is data that is coming out of a companion part of the AHRQ…I'm trying to…I forget what the acronym is. Is it decide? It may be decide, but of which their evidence based practice centers are one part of it and then there's this other group that is supposed to do rapid turnaround original analysis and so the third bullet point is based on observational data, analysis of claims data…of drug utilization data. And in that analysis, conventional antipsychotics are also associated with this increased risk of death in elderly patients with dementia and agitation. These are data that I believe come from British…an analysis of British Columbia…a British Columbia database. You guys may be more familiar with it than I am. HRQ forwarded three abstracts to us and asked us to include that in the report and that's where this comes from. And then the last high point in terms of the adverse events is there is insufficient evidence to compare the risk of atypical antipsychotics with that of typical antipsychotics for inducing extrapyramidal side effects or tardive dyskinesia in patients with off label conditions. Okay? Obviously they are data from the…from the CADI(?) trial and from other things about the head-to-head comparisons of patients with schizophrenia. All right? And your group will need to make the decision about the degree to which those data are generalized for the other group.

Last slide. The key question three about subpopulations, well as you can see from the data that we presented there is very little evidence here to begin with and so trying to find evidence in subpopulations when you only have 3 or 5 or 6 studies to begin with was not possible and the same thing about dosing and time limits. The data are just too thing for that.

So then the last slide in this group. The summary…there is some evidence of benefits for behavioral disturbances in dementia, OCD and autism. The second bullet point, although there is no difference in eight weeks there is perhaps the onset of recover is faster in patients with treatment resistant depression if augmented with atypical antipsychotics. And I put a question mark behind that because I don't think that that is at the level that the first bullet point is at. The third bullet point there is really too few trials that say with any conviction anything about sort of all the others. All right? There is no obviously long-term for these things. There is the increased risk of death that we talked about in patients with dementia. The increased weight gain with olanzapine and then importantly the data…there's just more trials in general for risperidone and olanzapine and the least for aripiprazole and ziprasidone and so that can affect…that may be one thing that you would take into consideration when trying to judge the strength of the evidence for individual drugs.

So that brings that to the end and I guess now it's time for questions.

Dan Lessler: Great. That is a great review. So I'm going to open it for…

Paul Shekelle: I can barely hear you. Can you speak up or get down to the microphone?

Dan Lessler: That was a terrific presentation and review of the data and I think now we'll open it up to committee members for questions and comments.

Bob Bray: This is Bob Bray. The question I had was the…reviewing the evidence of the off label use for personality disorders because that covers such a wide range of patients. Was there a predominant personality disorder that was evaluated or…

Paul Shekelle: I would have to double-check that. If you can give me…why don't we take the next question and I should be able to find that out for you in a minute.

Dan Lessler: Are there questions…

Vyn Reese: This is Dr. Reese and the question is was there any difference between the agents in risk of stroke in the elderly with medication? Was it a higher risk in risperidone or…

Paul Shekelle: Yeah, right. Well, that goes to that Canadian study and so there is the Canadian study that reported exactly that. I don't…out of the JAMA(?) article, of course, didn't quite break it down that way. I think that that is…my own view of that is…we didn't comment on that one way or the other, other than to note that there is that Canadian report that concluded that it was…that increased risk of cardiovascular death was a stroke and it was risperidone specific. My own view is that that…taking that one to the bank is premature at this point.

Dan Lessler: Are there other questions?

Man: It looks like you did not look at anxiety disorders then?

Paul Shekelle: Correct. Okay. Now if you can bear with me here. Here is the study that figured into the personality disorders. There were five [inaudible]. Let's see, first study was 28 women with borderline personality disorders, second study was also borderline personality disorder, third study was borderline personality disorder, fourth study was also borderline and fifth was schizotypal personality disorder. So I guess four borderlines and one schizotypal or schizotypal. Did I pronounce that right? Does that help answer your question?

Bob Bray: Yes, thank you.

Paul Shekelle: Okay.

Dan Lessler: Are there other comments or questions…Alvin?

Alvin Goo: Hi, it's Alvin. You mentioned that one of your studies had an end of 25. Is that the typical number on these studies?

Paul Shekelle: Whoever is asking the questions is either going to have to get closer to the microphone or have somebody close repeat it because I can hear something going on, but I can't hear the question.

Alvin Goo: Hi, it's Alvin. Can you hear me?

Paul Shekelle: Yeah, now I can hear.

Alvin Goo: So you mentioned at the end of one of the studies the number 25.

Paul Shekelle: That's a typical end for most of these studies outside of the dementia studies.

Alvin Goo: Okay, thanks. With the patients with depression…were there any breakdown of patients with depression and psychosis or, you know, any further categorization of those patients?

Paul Shekelle: Yes, there was as a matter of fact and the depression one was the one where we had the hardest time trying to keep apples with apples and oranges with oranges and, you know, that initial…in our initial draft report we actually sort of pooled across these conditions and we got our hands slapped by our pier reviewers saying that you have to keep these guys separate. It sort of breaks down into a…the depression studies sort of break down in the following.

Man: …combining all of those or…

Paul Shekelle: No, no. We had to deal with them all separately and unfortunately we're not able to pool anything in that because there's just not enough poolable data.

Man: So then the comment in terms of lack of effectiveness would be stratified, but…in the nine studies in treatment resistance…no effect that you could find two studies to make an impression with psychosis…

Paul Shekelle: Right, right. So for the major depression with psychotic features there were two studies. Okay? In one of them they gave olanzapine compared to olanzapine…[inaudible] compared to placebo. Okay? And this was kind of a…it was one report and in one trial they had 124 patients and in the other trial they had 125 patients and in one of those two trials they reported a benefit and in the other trial they didn't report a benefit. So, you know, sort of within the same report there were two trials, which reached conflicting conclusions. Okay? Then for the augmentation one where they had…to get into the study you had to have SRI resistant, generally SRI resistant. Sometimes [inaudible] resistant depression. There is a table, which is table 3 in the report that sort of summarizes all of those studies. And rather than me try to mangle that over the phone it's probably best if you just review that, but the take home that I got from that was that if there was a benefit it had more to do with the…and I'm not saying this is proven, but there is a suggestion that had more to do with the onset of improvement rather than sort of the subsequent, you know, end result.

Dan Lessler: I guess my other question then in terms of…was there any way to comment on the power…you guys were doing meta-analysis then?

Paul Shekelle: Well, no. We weren't able to do meta-analysis on that and if where you're going is is can you say it's not effective? The answer is no. That's, you know, most of these things are not powered sufficiently to exclude potentially clinically important

effects. That's why you see in our conclusions lots of inconclusive and not no evidence of benefit.

Dan Lessler: So in some sense in terms of, you know, I guess the reason for doing this is it is obviously thinking about how can this…how can what you've gathered be useful in terms of informing any approach that MAA may take to sort of improving the prescribing of these medications off label. It seems like perhaps…actually, let me bounce this off of you then. So on the one hand it seems reasonable perhaps to conclude where we see the, you know, that there appears to be some benefit that, you know, sometimes a positive outcome, you know, it's something that, you know, I guess in some sense we can run with, you know, somewhat more confidently but where there is no benefit it's hard to know how to translate that into sort of, you know, relevant policy or intervention on the part of MAA in terms of improving the appropriate utilization of these medicines.

Paul Shekelle: Yeah, well, this is why they pay you guys the big money presumably to be on this committee, because I agree those are very tough policy decisions. And if it had to do with whether, you know, when there is little evidence to either conclude or exclude a benefit, what do you do?

Dan Lessler: Do you want to comment?

Man: Well, first of all it's for all the agencies, not just MAA and, you know, of course we talk…I'm not saying it's completely an [inaudible]. The [inaudible] we took with the NIA epileptic drugs for pain was that there was pretty good evidence in for…say neurontin and several kinds of neuropathy. There was not a lot of study in every neuropathy, but because it worked in two or three different neuropathies we more or less concluded it could work in just about every kind of nerve pain, but on the other hand there was no evidence for usefulness of anti epileptic for pneumatic pain or back pain or chronic pain and we made a policy decision, all of us, and then we passed it by you guys that that wasn't reasonable, that it wasn't reasonable to keep spending a lot of money on neurontin for pack pain and in fact L&Is major neurontin bill was for back pain, not for radiculopathy, not for nerve pain. So I'm wondering whether there might be an analogous way to approach this data as we move forward with the mental health sub committee and other experts on this committee and the agencies in making these decisions in the future.

Dan Lessler: That's a good point. I'm wondering if there are other comments or questions from committee members in talking about working with this data?

Vyn Reese: This is Dr. Reese. I want to make certain…I certainly understand that the effects in depression you said that it was…they worked…there was some evidence that showed that there was augmentation in depression that they perhaps speeded up the response of an antidepressant or by themselves they did that, but then psychotic depression they didn't seem to have any effects at all, which would be the logical place where they would seem to have an effect. Is that correct? They were…the data we have we didn't see any positive or no positive trial?

Paul Shekelle: Yeah, well, there's only two studies that we identified that were treatments of major depression with psychotic features and they came to these somewhat conflicting results. Okay? For the patients that had treatment resistance…okay? And so these are generally all studies that…where patients…there was a run in period of, okay, several weeks. So first they were somehow referred into the study to begin with and then they did a run in of several weeks on treatment with an SRI or with venlafaxine and then they selected the people that didn't have a response at four weeks and then they randomized those guys to continue that medicine and then either get an atypical antipsychotic or get placebo. Okay? And so that's how those studies tended to work. I mean that's an over generalization, but that's sort of what it looked like. And if you look at those studies three of those studies, of those 8 or 9 studies, reported no difference at the final outcome point, but reported that the onset was faster with the…onset of recovery was faster for some outcome measures in the patients that got the augmentation therapy. But all of these studies, you know, looking through them they have three, four, five different outcomes. Right? And so…and they have multiple different time points and they're reporting, you know, some positive here, some not positive there. I would characterize all of them as saying there is no real strong signal, which means…by that I mean that it is a consistent finding that happens across all outcome measures and across studies. All right? There is a suggestion of this possible earlier onset, but it's not at the level of the evidence that some of the other conclusions that we have, you know, it's not that same strength of evidence.

Dan Lessler: Are there other questions or comments for Dr. Shekelle? I'm going to turn to Gary and Siri at this point because actually I'm looking at the way…specifically the agenda says an expected outcome is that the DUR board approval of atypical antipsychotic off label use criteria.

Man: That was a mistake. I think it was related to the criteria…safety criteria before, right?

Dan Lessler: Oh, okay. All right. Okay.

Man: There was not intended to be any decision today. We will go forward with discussions with the mental health sub groups and others on this information presented by Dr. Shekelle.

Dan Lessler: And I think that would be…that's what would be helpful is for it to go back to the mental health subgroup to work and then to come back with a set of recommendations that we can evaluate. I think it's very helpful to have Dr. Shekelle's, you know, presentation and this discussion for us is background in terms of being able to sort of digest those recommendations.

Man: Paul, thanks very much. It was very, very helpful for you to come on today and we appreciate the good value.

Paul Shekelle: Okay. My pleasure you all.

Man: All right. We'll have a great dinner.

Paul Shekelle: Okay. Bye now.

Man: Just one more thing. I think it's just great that we got the federal government to be able to fund this one systematic review. These do tend to be fairly, you know, resource intensive and expensive and, you know, maybe we can do some other ones in the future. I don't know how much money they have left, but…Dr. Shekelle is at the top of the field in doing these systematic reviews. He's excellent and so I'm really glad they assigned it to RAND and that he was the presenter today.

Dan Lessler: Yeah, thanks a lot. I agree. It was a really well done analysis and presentation and very helpful. So Siri at this point do you…we've already discussed that it's going to go back to the mental health subgroup to take up in terms of recommendations to come back. Is there anything then that we…

Woman: And the agency medical records.

Dan Lessler: And the agency medical records. Right.

Siri Childs: Yes, this should be considered just informational at this point in time and to kick off our next, you know, work group commitment to come back with recommendations for off labeled use.

Man: Is there going to be more off labeled uses examined than there were here in the report?

Siri Childs: [inaudible]

Man: [inaudible] other off labeled uses [inaudible] other systematic reviews and we haven't talked about that.

Man: Yeah, yeah.

Man: [inaudible] resources into looking at others and I guess what I would recommend is [inaudible] see maybe [inaudible] because there's a lot of data here, these are tough decisions and I'd like to see how, you know, this [inaudible] go. Whether we can come up with some policy relevant decisions. [inaudible] the group and HC medical director before we decide and put a lot more resource into any additional [inaudible] systematic [inaudible] the resource.

Dan Lessler: That sounds like a good beginning and see how it all works from a policy standpoint.

Man: Off labeled use [inaudible] we weren't able to capture any data or information on subpopulations. For instance substance abusers.

Dan Lessler: Unfortunately, Dr. Shekelle…maybe we could ask him specifically but it sounds like that was not something they were able to address in his opening.

Bob Bray: This is Bob Bray. It's strikes me also that, you know, the comment that…not finding efficacy in the evidence does not mean that it is not efficacious or that it couldn't be used and so I think we have to, hopefully as we move forward with that we don't use the lack of information to avoid something as opposed to taking that lack of information and figuring out how does that…what does that mean for its use? So I think those are two kind of distinct issues that we should be careful about. Some of these things I could see that there may be some reasonable alternatives for use, but there's others that there may not be very many alternatives if you're trying to help the patient pharmacologically. So I think that we should take that into account.

Dan Lessler: Any other comment or discussion from the committee? So I think that concludes that there is…looks like we've gone through agenda and so I thank everybody and we can…Jeff, did you have any other comments before we adjourn or anything like that?

Jeff Graham: Well, we believe our next meeting is at this same place and that's in August, but we're pretty sure it's here. Regina's not here today, but we're pretty sure it is.

Dan Lessler: All right. So thank you and we're adjourned.